VIEWS ON SCIENCE POLICY OF THE NOBEL LAUREATES FOR 1985

HEARING

BEFORE THE

COMMITTEE ON SCIENCE AND TECHNOLOGY U.S. HOUSE OF REPRESENTATIVES

NINETY-NINTH CONGRESS

SECOND SESSION

MAY 21, 1986

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VIEWS ON SCIENCE POLICY OF THE NOBEL LAUREATES FOR 1985

WEDNESDAY, MAY 21, 1986

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE AND TECHNOLOGY,
Washington, DC.

The committee met, pursuant to call, at 2:10 p.m., in room 2318, Rayburn House Office Building, Hon. Don Fuqua (chairman of the committee) presiding.

The CHAIRMAN. It is a special privilege and honor to welcome today to the Committee on Science and Technology the Nobel Laureates in Science for 1985.

American science has made tremendous strides since the new policy of Federal support for scientific research was inaugurated with the Bush Report in 1945. From the beginning, a nation which in earlier decades looked to Europe for leadership in research, we have become a nation which in itself is in the leadership position. Nothing more clearly indicates that position of leadership than the long line of American scientists which have gone before you as Nobel Laureates in science.

We congratulate you on the outstanding scientific research which has led to the recognition by the Swedish Academy and, through the Academy, by your scientific peers here and abroad.

We welcome you for another reason as well. You are yourselves, in spite of the fame and fortune which has come your way, still active bench scientists. In a very real sense you are the frontline workers in science, and the beneficiaries of the massive apparatus of Federal support for science.

As the ultimate beneficiaries of that system, you may be able to give us a new and special perspective on how well, or how badly, for that matter, that system is working. We would welcome your comments on any and all aspects of the Government's policies and practices for the support of research.

I extend a special welcome to the spouse of one of our laureates, the wife of Dr. Jerome Karle, Dr. Isabella Karle. We are aware of your close scientific collaboration over the years, and we appreciate your willingness to join us for this occasion.

If you would take your respective seats at the table, we would be delighted to hear from you, and then at the end we will have some questions. And as I had mentioned to some of you prior to the meeting, I am sure we will be interrupted at some point during the hearing. Our first witness will be Dr. Jerome Karle of the Naval Research Laboratory here in Washington.

First of all, Mr. Packard, do you have any statement?

Mr. PACKARD. No, Mr. Chairman, I am just delighted to meet with such a distinguished group of scientists. It is almost intimidating to have before us such a brilliant group of people, and we are honored to have you with us, and we are looking forward to your testimony.

The CHAIRMAN. Thank you.

Dr. Karle?

[Additional information follows:]

Information

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The Royal Swedish Academy of Sciences has decided to award the 1985 Nobel Prize in Chemistry to Professor Herbert A. Hauptman, The Medical Foundation of Buffalo, USA, and to Professor Jerome Karle, US Naval Research Laboratory, USA, for their outstanding achievements in the development of direct methods for the determination of crystal structures.

Summary

This year's Nobel Prize in Chemistry has been awarded to Herbert A. Hauptman and Jerome Karle "for their outstanding achievements in the development of direct methods for the determination of crystal structures". The prize is being awarded for a methodology because of the great importance of this methodology for chemical research. Through Hauptman's and Karle's fundamental achievements, the methods have been developed into practical instruments for determining the structure of molecules within both inorganic and organic chemistry - not least within the chemistry of natural products.

The determination of structure involves generating a three-dimensional picture of the positions of the atoms. The picture maps the electron density within the crystal: the density is greatest at the centre of the atoms. It can never be less than zero anywhere, and this is the fact upon which the Hauptman-Karle method is based.

Structure determination employs radiation of so short a wavelength that it becomes possible to "see" the atoms - X-rays are normally used for this. This means that the wavelength must be shorter than the distance between each atom. X-rays striking a crystal are deflected and concentrated in different directions, and the intensity of the deflected rays is measured. In order to determine the positions of the atom in a crystal, however, is it not enough to know the direction and intensity of the rays, it is also necessary to know the "phase" of each deflected ray, that is, how much the waves in the different rays are displaced in relation to each other.

KUNGL.
VETENSKAPSAKADEMIEN
THE ROYAL SWEDISH
ACADEMY OF SCIENCES

16 October 1985

The fact that electron density is positive (electrons either exist or they do not) limits the possibilities for phase displacement. Hauptman and Karle have constructed systems of equations that are based on the values of the intensities measured and that describe the limitations. The two scientists have also developed a procedure for solving the equations: the solutions give direct connections between the phases sought.

Since the validity of each equation is only statistically probable, it is necessary to make a large number of measurements and to obtain many times more equations than the number of unknowns to be determined. While this makes the determinations of phase more reliable, it entails comprehensive calculations of the kind that are now feasible using modern computer techniques.

The method is termed "direct" because of the fact that, in contrast with other methods, it gives the structure directly from the data collected.

In order to understand the nature of chemical bonds, the function of molecules in biological contexts and the mechanism and dynamics of reactions, knowledge of the exact molecular structure is absolutely necessary.

Background Information

This year's Nobel prizewinners in Chemistry, Herbert A. Hauptman and Jerome Karle, have developed what are termed "direct methods" for the determination of crystal structure. This development of a method merits a Nobel Prize since the method now plays an increasingly important role in chemical research. It is therefore of importance to consider the method first.

As early as the turn of the century, chemists possessed a good understanding of the geometrical arrangement of the atoms in carbon compounds. But it is only through structure determination using X-ray crystallography that we have been able to obtain a detailed picture of the distances between the atoms and of the angles between the various bonds. Spectroscopy and electron diffraction have played a complementary role, especially in the case of simpler molecules.

Until the 1960's it was determination of the arrangement of the atoms that gave the most important new results. The whole of inorganic chemistry was revolutionized, hitherto completely unknown principles of stucture being elucidated. Important progress was also made in natural product chemistry. A series of Nobel prizes describes this development: von Laue in 1914, the Braggs, father and son 1915, Pauling 1954, Perutz and Kendrew 1962, Crick, Watson and Wilkens 1962, Hodgkin 1964, Barton and Hassel 1969, Lipscomb 1976 and Klug 1982.

Lipscomb combined structure determination with far-reaching studies of the nature of chemical bonds, and it is precisely this theory of chemical bonding that requires knowledge of the exact structure of molecules - in other words, accurate bond distances and accurate bond angles.

The need for exact knowledge of structure is great within two areas of chemistry. One of these areas concerns structural problems, especially those associated with the function of molecules in biological contexts. Here, a large number of processes are considered in similar ways under the heading "signal - receptor processes". Examples of these processes are enzyme activity, antigen - antibody and scent substance - scent receptor. For understanding these signal-receptor processes it is necessary to gain as detailed a knowledge as possible of both signal molecules and receptor molecules (active site). The signal molecules are relatively small and their structure can be determined. The structure of the receptor molecule can also be perceived by analogy with low-molecular compounds. Where giant molecules are involved, structure determination of the type for which Perutz and Kendrew received a Nobel Prize is required. For determining the low-molecular signal molecules the Hauptman-Karle direct method must be used.

In the other important area, the mechanism and chemical dynamics of reactions are studied. Questions being asked also by chemists working with organic synthesis are, for instance: How, at molecular level, does a chemical reaction take place? How does a molecule move, and how is the structure changed in chemical reactions? The most important answers are coming from researchers within theoretical chemistry, but these must in turn have accurate knowledge of the structures of reacting molecules.

To summarize: the last fifteen years have seen a large increase in structure determinations accomplished within both inorganic and organic chemistry, including natural product chemistry. These determinations have been carried out predominantly using "direct methods". Looking into the future we can predict a further increased need for structure determinations of this kind.

While it is easy to explain the importance for chemistry of the two prizewinners' development of the methods, it is condsiderably more difficult without recourse to mathematical formulae to describe the achievement itself in a way that is easy to understand.

When X-rays strike a crystal, they will be deflected only in certain definite directions, where the intensity of irradiation may be measured. To determine the arrangement of atoms in a crystal, however, it is not enough to know the direction and intensity. The "phase" of each ray so deflected must also be known. In special cases, it has been possible to solve this "phase problem" by making use of the fact that "heavy" atoms containing many electrons spread the X-rays more strongly than "light" atoms do. This property of heavy atoms is used both in "Patterson methodology", which has been very important in structural inorganic chemistry, and in "isomorph substition". The latter is used when determining the structure of giant molecules such as proteins. In this case the heavy atoms can be bound to the protein without its structure being appreciably altered. This however is not possible for the large number of compounds.

Two facts have created the conditions for the development of the "direct" methods. The first is that electron density, which diffuses the X-rays, can never be negative. The other is that the number of measurements is much greater than the number of equations to be solved, which permits the use of statistical methods. In work done between 1950 and 1956, Hauptman and Karle laid the foundations for a rational exploitation of these possibilities, specially the use of inequalities.

The immense importance of this work for subsequent development may easily be followed in the literature. This is not to say that Hauptman and Karle alone are responsible for the development, and other names must be mentioned in particular. Before Hauptman and Karle published their work, D. Harker and J.S. Kasper proposed the use of one inequality, which represents a special case in the Hauptman-Karle system, and determined a complicated structure using it. Important conceptual contributions were also made by D. Sayre, who anticipated the practical approach which has later come to be used. Isabel Karle's and M. Woolfson's contributions to the practical utilization of direct methods have been crucial, and in this connection the development of fast computers has been a prerequisite for the full realization of the value of the method.

Herbert Aaron Hauptman

Born in New York, NY, USA, 14 February 1917.

Ph.D., University of Maryland, 1955. Professor of Biophysics, State University of New York, Buffalo, since 1970.
Director of Research and Vice President of the Medical Foundation of Buffalo since 1972.

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Jerome Karle

Born in New York, NY, USA, 18 June 1918.
Ph.D., University of Michigan, 1943.
Professor at the State Department of Health, New York, 1939.
Director of Research, Laboratory for Structure of Matter, US Naval Laboratory, Washington, since 1967.

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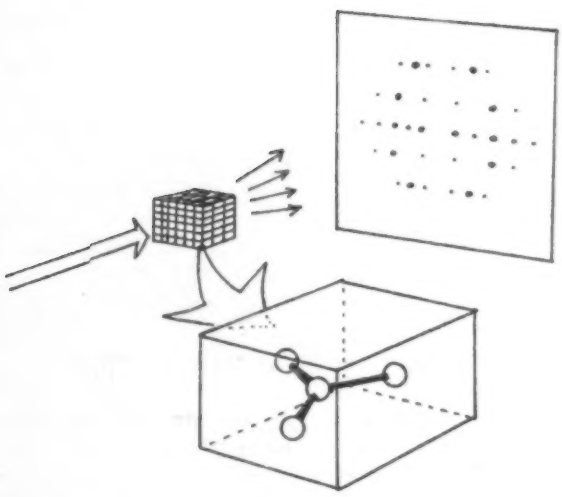

Röntgenstrålar faller in mot en kristall. Kristallen innehåller en molekyl som upprepas genom hela kristallen i alla riktningar. Kristallen sprider röntgenstrålningen i vissa bestämda riktningar, så att olika starka fläckar erhålls t ex på en fotografisk film. För strukturbestämning måste också fasen bestämmas för varje fläck. Detta sker med de direkta metoderna.

X-rays strike a crystal. The crystal contains a molecule, which is repeated throughout the whole crystal in all directions. The crystal deflects the x-rays in certain definite directions so that the radiation can be seen as spots of different intensity such as in a photographic film. To determine the structure the "phase" of each ray that is deflected must also be known. This determination can be carried out by using the "direct methods".

STATEMENT OF DR. JEROME KARLE, LAUREATE IN CHEMISTRY, AND DIRECTOR OF RESEARCH, LABORATORY FOR STRUCTURE OF MATTER, NAVAL RESEARCH LABORATORY, WASHINGTON, DC

Dr. JEROME KARLE. Mr. Chairman, members of the committee:

I am pleased to have the opportunity to speak about some matters that I feel are important for the progress of science in our society. They concern some aspects of the practice of scientific research, particularly with respect to Government laboratories, some considerations relevant to the encouragement of young, talented people and the profound effect that funding agencies can have on the progress of areas of research.

There are many aspects to a supportive environment in a research institution. They include:

One, the availability of large amounts of time to concentrate on the research program of interest without interruption;

Two, the availability of funds for the purchase of equipment, generally as needed, and fine engineering and shop facilities to produce equipment when it is not commercially available at affordable cost;

Three, service groups such as purchasing and public works that are geared to serve the community of scientists in a timely, efficient and cooperative fashion;

Four, an absolute minimum of administrative distractions;

Five, a sensitivity to the motivations and viewpoints of creative scientists;

Six, the provision of a dignified environment in which not only the efforts and successes of creative scientists are acknowledged but also their personal dignity is preserved;

Seven a competitive pay scale that permits an economically secure and respectable existence; and

Eight, tenured job opportunities as the rule rather than the exception.

It is possible to carry out good science and still satisfy the requirements of mission-oriented government laboratories. I, nevertheless, have the perception, largely from my contacts with numerous colleagues, that the quality of the working environment in various government laboratories has diminished in recent years.

I do not know all the reasons for this, but some concern the increasing tightness of funding, the current mechanisms for funding, what I regard as overemphasized attempts to make sure that marginal employees do not remain so, reacting to unethical behavior in a way that implies that no one is to be trusted and a broad misunderstanding of how creative scientists are motivated, how research proceeds and how productivity may be evaluated.

The tightness of funding is a fact of life with which everyone is quite familiar. What can be hoped for is that the resources that are available would be allocated in such a way that would reflect well on the Government's perception of priorities.

There are many instances of multiple sources of funding for laboratories. The disadvantages concern the need for a senior scientist to spend inordinate amounts of time to acquire adequate funding, yearly uncertainties in funding, loss of control of the direction of

the research program, and difficulty in carrying out long-range high-risk research that could lead to major advances.

The advantage of multiple-source funding is the decrease in sensitivity to the deterioration of any one source. I believe that the weighing of advantages and disadvantages suggests that in most cases the optimal situation would derive from having one major source of funding an perhaps some additional minor sources.

In addition, a strong case can be made for funding over greater periods than 1 year, at least 2 years or more. The real world of funding acquisition and contracting and purchasing within the 1 year framework has led to circumstances that are not conducive to the most effective pursuit of research programs.

In the well-motivated attempt to enhance the quality of performance, especially among the marginal performers in the Federal Government, personnel, administrative and evaluation techniques have been developed that are not well attuned to the motivations of creative scientists or the manner in which scientific research progresses. This is an area in which I would strongly advise that the opinions and advice of research scientists be sought and taken seriously.

One of the implications that is especially rankling is the implication that dedicated research scientists are motivated to improve their efforts or do their best work because it may give rise to a monetary bonus at the end of the year. Badly designed administrative systems can eventually distill from an organization the best people and leave those who are more less attuned to the system. The residual personnel under such circumstances are not likely to be the scientifically most creative.

Simply stated, the desirable, highly motivated scientists are people who are dedicated to their profession and cannot wait to get to their workplaces each day. They often devote large amounts of personal efforts to their profesion without compensation in terms of extensive out-of-hours efforts that may involve, for example, additional research, the review of manuscripts for publication, the review of research proposals, committee participation, communication with fellow scientists, and efforts associated with the planning and organizing of scientific meetings.

All aspects of scientific and technical effort should be kept strong, academic, Federal and industrial and tendencies that weaken any of them are highly undesirable.

I must say that several Federal laboratories with which I am familiar have seen a better day in terms of personnel morale, productivity and resources for conducting creative research. I believe that anyone interested in restoring and enhancing the Federal laboratory system should consider seriously items No. 1 through No. 8 that I listed above.

When I joined the Naval Research Laboratory, there was a strong desire among the leaders in the laboratory to achieve very high standards in creative research. I believe that they succeeded in many areas. They summarized their philosophy in a single, straightforward statement, "Find a good person and support him or her." This statement characterizes the spirit of items 1 through 8 and I, for one, was greatly benefited by it.

It is my perception that the dedication of the leadership at the Naval Research Laboratory, and undoubtedly other Federal laboratories, to the achievement of very high levels of creative research continues. The constraints imposed on Federal laboratories in recent years, however, appear to make it more difficult to establish such goals.

On the subject of attracting young talented people to a career in science, there is an aspect of the real world that plays an important role, but is rarely emphasized. It is the matter of a shortage of truly permanent or tenured jobs in areas that are valuable to the progress of science and could otherwise attract good personnel.

The general availability of worthwhile positions in particular professions is a type of information with which young people soon apprise themselves and it strongly influences their decisions concerning their careers. In the recent past, the professions of accountancy and medicine were extremely popular among students because they implied a secure and well-paying future.

It is very fine to increase support for general education and for graduate and postdoctoral training. Excellent as they are, such efforts do not get to the heart of the matter. In fact, the present availability of postdoctoral appointments and various temporary arrangements only exacerbates the problem. They replace proper employment and often lead people into middle age without affording them the opportunity for a secure and settled future. It is difficult to have an economically satisfactory and properly organized family life under such circumstances.

We need to have good, more secure positions in scientific research that are available at a time when a creative person is most enthusiastic and often most productive. The fact that such positions are often not currently available to large numbers of highly qualified young people is quite apparent to me from my contacts with governmental laboratories and educational institutions.

The difficulty in finding good positions is the type of information that flows down through the school systems very rapidly. Without the existence of reasonable opportunities to fulfill one's aspirations for the future, young people are discouraged from making the large-scale, self-sacrificing effort required for the adventures that modern science has to offer.

In one aspect of the reaction to this, many scientifically qualified students have chosen more lucrative professions instead of taking graduate studies in, say, chemistry or physics.

I am, of course, aware of the fact that certain areas of science are from time to time heavily supported, so that if one is presently, for example, a computer expert or a genetic engineer, opportunities abound. However, it is important to maintain a balance among scientific fields and at present there are increasing omissions and dislocations.

My own field of crystallography offers—affords—many such examples. Since the 1970's, for example, support for significant areas of the field has been diminishing—for example, small molecule crystallography. Faculty positions and graduate students have been disappearing, the subject is rarely taught and the United States has been relatively less productive compared with the rest of the world.

I say this with some authority since I chaired expert committees in 1975 and 1982 that prepared reports for the National Science Foundation concerning the status and future potential of crystallography.

I shall return shortly to the matter of balance of support in science. The question of what to do to make the job market more attractive to young people remains unsettled. I realize that this is not an easy problem with easy solutions since it could be costly at a time when funding is difficult. I have one suggestion, however, that may not be so costly.

There are vast Government sums that are spent on research programs involving nonpermanent, untenured employment. The Government could take the lead in requiring that such practices be greatly diminished in favor of working through organizations or arrangements that involve positions having permanent status with pay at a competitive level. If the Government would take such a lead, other research institutions may feel that they have to follow suit.

There are other ways to make a career as a scientist attractive. These were outlined at the beginning of my presentation and concern not only personal income, but support in its broader aspects and the quality of the working environment.

My final remarks concern the value of maintaining a reasonable balance of support throughout the sciences. I believe that most people would agree to the virtue of doing so. The problem arises from the proliferation of new areas of science and constraints on funds available. There is then the tendency to ask what the most important areas for support might be. The purpose of the question is usually to help determine the future emphasis of support, but in practice the emphasis has a tendency to be so strong that whole areas may tend to be neglected. This is a very difficult problem because all aspects of it are subject to interpretation. What is a balanced program?

There is a feature of significantly diminishing support in a scientific area that may be termed "erroneous justification." Diminishing support will cause researchers to seek funding in other areas or none at all after a period of time. This drives professionals and students from the area and after a while there appears to be little activity or interest. The latter result can then be used to justify the diminished support.

I do not know precisely what a balanced program is. One could hope that funding agencies would monitor the trends in their funding and be concerned about broad shifts in activity over the years that are not easily explained or understood. Perhaps they do that. I have some evidence, however, in my own field that very fine proposals were not funded and a considerable diminishing of some areas were allowed to take place.

There always seem to be more problems than solutions. I appreciate very much the efforts of the committee to apprise themselves of current issues affecting the progress of science and their interest in pursuing such problems. I hope that I have said something that is useful to you.

Thank you.

[The prepared statement of Dr. Jerome Karle follows:]

Testimony of Jerome Karle before the Committee on Science and Technology,

U. S. House of Representatives

May 21, 1986

Mr. Chairman, members of the Committee, I am pleased to have the opportunity to speak about some matters that I feel are important for the progress of science in our society. They concern some aspects of the practice of scientific research, particularly with respect to government laboratories, some considerations relevant to the encouragement of young, talented people and the profound effect that funding agencies can have on the progress of areas of research.

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(7) A competitive pay scale that permits an economically secure and respectable existence.

(8) Tenured job opportunities as the rule rather than the exception.

It is possible today to carry out good science and still satisfy the requirements of mission-oriented government laboratories. I nevertheless have the perception, largely from my contacts with numerous colleagues, that the quality of the working environment in various government laboratories has diminished in recent years. I do not know all the reasons for this, but some concern the increasing tightness of funding, the current mechanisms for funding, what I regard as overemphasized attempts to make sure that marginal employees do not remain so, reacting to unethical behavior in a way that implies no one is to be trusted and a broad misunderstanding of how creative scientists are motivated, how research proceeds and how productivity may be evaluated.

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All aspects of scientific and technical effort should be kept strong, academic, federal and industrial and tendencies that weaken any of them are highly undesirable. I must say that several federal laboratories with which I am familiar have seen a better day in terms of personnel morale, productivity and resources for conducting creative research. I believe that anyone interested in restoring and enhancing the federal laboratory system should consider seriously items (1)-(8) listed above.

When I joined the Naval Research Laboratory, there was a strong desire among the leaders in the laboratory to achieve very high standards in creative research. I believe that they succeeded in many areas. They summarized their philosophy in a simple, straightforward statement, "Find a good person and support him (her)." This statement characterizes the spirit of items (1)-(8) and I, for one, was greatly benefited by it.

It is my perception that the dedication of the leadership at the Naval Research Laboratory, and undoubtedly other federal laboratories, to the achievement of very high levels of creative research continues. The constraints imposed on federal laboratories in recent years, however, appear to make it more difficult to accomplish such goals.

On the subject of attracting talented young people to a career in science, there is an aspect of the real world that plays an important role, but is rarely emphasized. It is the matter of a shortage of truly permanent or tenured jobs in areas that are valuable to the progress of science and could otherwise attract good personnel. The general availability of

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The difficulty in finding good positions is the type of information that flows down through the school systems very rapidly. Without the existence of reasonable opportunities to fulfill one's aspirations for the future, young people are discouraged from making the large-scale, self-sacrificing effort required for the adventures that modern science has to offer. In one aspect of the reaction to this, many scientifically qualified students have chosen more lucrative professions instead of taking graduate studies in say chemistry or physics.

I am, of course, aware of the fact that certain areas of science are from time to time heavily supported, so that if one is presently, for example, a computer expert or a genetic engineer, opportunities abound. However, it is important to maintain a balance among the scientific fields and at present there are increasing omissions and dislocatons. My own field of crystallography affords many such examples. Since the 1970's, for example, support for significant areas of the field has been diminishing (e.g. small molecule crystallography), faculty positions and graduate students have been disappearing, the subject is rarely taught and the United States has been relatively less productive compared with the rest of the world. I say this with some authority since I chaired expert committees in 1975 and 1982 that prepared reports for the National Science Foundation concerning the status and future potential of crystallography.

I shall return shortly to the matter of balanced support in science. The question of what to do to make the job market more attractive to young people remains unsettled. I realize that this is not an easy problem with easy solutions since it could be costly at a time when funding is difficult. I have one suggestion, however, that may not be so costly. There are vast government sums that are spent on research programs involving temporary or, at least, nonpermanent employment. The goverment could take the lead in requiring that such practices be greatly diminished in favor of working through organizations or arrangements that involve positions having permanent status with pay at a competitive level. If the government would take such a lead, other research institutions may feel that they have to follow suit.

There are other ways to make a career as a scientist attractive. These were outlined at the beginning of my presentation and concern not only personal income, but support in its broader aspects and the quality of the working environment.

My final remarks concern the value of maintaining a reasonable balance of support throughout the sciences. I believe that most people would agree to the virtue of doing so. The problem arises from the proliferation of new areas of science and constraints on funds available. There is then the tendency to ask what the most important areas for support might be. The purpose of the question is usually to help determine the future emphasis of support, but in practice the emphasis has a tendency to be so strong that whole areas may tend to be neglected. This is a very difficult problem because all aspects of it are subject to interpretation. What is a balanced program?

There is a feature of significantly diminishing support in a scientific area that may be termed "erroneous justification". Diminishing support will cause researchers to seek funding in other areas or none at all after a period of time. This drives professionals and students from the area and after a while there appears to be little activity or interest. The latter result can then be used to justify the diminished support.

I do not know precisely what a balanced program is. One could hope that funding agencies would monitor the trends in their funding and be concerned about broad shifts in activity over the years that are not easily explained or understood. Perhaps they do that. I have some evidence, however, in my own field that very fine proposals were not funded and a considerable diminishing of some areas were allowed to take place.

There always seem to be more problems than solutions. I appreciate very much the efforts of the Committee to apprise themselves of current issues affecting the progress of science and their interest in pursuing such problems. I hope that I have said something that is useful to you.

The CHAIRMAN. Thank you very much, Dr. Karle. We will now hear from your collaborator, Dr. Isabella Karle.

STATEMENT OF DR. ISABELLA KARLE, SENIOR SCIENTIST, NAVAL RESEARCH LABORATORY, WASHINGTON, DC

Dr. ISABELLA KARLE. Mr. Chairman and members of the Committee on Science and Technology, I welcome the opportunity to testify before this committee with respect to the Government's role in support of scientific research and education. I am honored to have been invited to appear with the American Nobel Laureates for the year of 1985.

My remarks will be general and qualitative and will reflect strong personal impressions from long experience in basic research. Creativity in science, as in other endeavors, is a difficult subject to define or to quantify. Individuals react and operate in various modes. There are, however, some basic requirements that should be fulfilled such as:

One, a good basic education in mathematics and the sciences at all levels of schooling. Exposure of all students to some scientific education is desirable, even necessary, so that the nonscientists can become responsible adults who can respond intelligently to the many issues that arise in our technical society and who can have empathy with the problems facing scientists.

Two, an atmosphere of social acceptance and recognition for the scientifically oriented students. The lack of acceptance of the serious students arises in part from too much emphasis in our high schools and colleges on nonacademic activities, such as extramural sports.

Three, a good environment to stimulate and sustain curiosity about the world around us at all levels of education and in the workplace.

And, four, this has been mentioned already. Reasonable job opportunities and security. Protracted periods of postdoctoral appointments, research associateships, and temporary appointments with the resultant disruption of both scientific continuity and of family life have their serious negative effects on morale and productivity.

As an aside, which I do not have in my prepared text, if students look at Chemical and Engineering News, there is almost a weekly report of some large chemical industry that has been decreasing the number of scientific positions, not by the tens, but by the hundreds and thousands of positions. And that certainly does not give a reason for students to continue their scientific or technical training.

And then five: Reasonable and steady funding for research. The nature of research makes it particularly vulnerable to instability. Wide oscillations in funding, and, at worst, interruptions in funding, result in long-term damage such as the dispersal of specialized scientific teams and technical personnel, the delay or abandonment of research programs, and the discouragement of potential students who are highly talented.

Given the above, I would like to discuss two topics in more detail. The first concerns the support of high-risk research which may be

defined by no immediate prospect of application or economic returns or even any prospects of solution to the problem.

In the spirit of Albert Michelson, the first Nobel Laureate in Science from the United States in 1907, who performed his first experiments on the velocity of light while an Ensign and an instructor in chemistry and physics at the Naval Academy following his own curiosity, instincts, and motivation. I urge that basic research and exploratory research, that is not particularly focused on some preconceived goal, receive its share of support.

Our present system of grants has built-in goals and objectives that have the tendency to lead to safe research, the kind of research that will satisfy the stated objectives and will ensure continued funding.

With the constraints imposed by this system, graduate students, postdoctoral researchers, and even senior investigators do not really have the freedom to pursue unorthodox and innovative ideas if they do not fall within the stated and approved objectives. Serendipity often plays a significant role. Scientists may recognize something that may be very important not directly related, but stemming from their other research. And there is the need to divert some of their time and resources to devote to these discoveries or thoughts. As often has been pointed out in the past, safe research would have led to a better iron lung. Innovative research produced the vaccine for poliomyelitis.

Furthermore, I should like to emphasize that good scientists with innovative ideas are found in a wide variety of institutions. Surveys have been conducted by the Citation Index, a publication that lists all the references in worldwide scientific literature made to papers published in scientific journals. Although the number of times a particular paper or a particular author is cited is a very imperfect measure, it nevertheless is an indicator of influential scientific papers and authors.

The recent collection of Citation Classics, that is, the most cited 250 papers over a period of 15 years, shows that the authors were employed by well-known universities, as well as smaller institutions of higher education, by Federal laboratories and national laboratories, by hospital research laboratories and private research institutes, and by industry. Except for industrial laboratories, where there may be severe constraints with respect to publications, all the other above-mentioned institutions were well represented.

A survey of the 1,000 most cited authors in the sciences showed a similar distribution of affiliations. I conclude from these surveys that good science has flourished in diverse institutions in the past and that the Federal budget for continuing support of basic science should continue to be directed to Federal laboratories, private research institutions, and universities.

The second topic that I should like to address is a period longer than 1 year for scientific budgets. The late Philip Handler, past president of the National Academy of Sciences, was an avid proponent for a 2-year budget period. And I should like to reemphasize the benefits of a longer period for budgets and grants in terms of efficiencies and economies.

The time of scientific investigators is extremely valuable. It should be spent primarily on research, and teaching, of course. At

present, principal investigators devote much of their time in the quest for obtaining money to support research. A longer budget or grant period would obviate the frequency of preparation of proposals and/or budgets.

The constraint of 1-year budget periods in which unexpended funds are lost to the investigator, and, in addition, future funding may be diminished since unexpended funds are viewed as unnecessary, make appropriate planning difficult.

Often the acquisition of major equipment is a lengthy process and a 1-year period is not sufficient for negotiations, delivery, testing, and acceptance. It would also be useful to be able to combine funds from 2 or more years' allotment for major procurement; an idea of saving for the future advocated by Professor Modigliani, who, unfortunately, is not here today.

The needs of a scientific project oscillate. The time of acquisition of equipment or instrumentation is often dictated by the availability of improved models in the relatively near future. Or the exchange of proposed equipment for a different type of equipment becomes apparent but time constraints of the budget will not allow it. The use of the computer for which charges are made varies depending upon the successes in experimental measurements in the laboratory. A longer budget period would allow greater flexibility, obviate purchases of inadequate instrumentation, and would result in greater economy in projects where the research results and needs are unpredictable.

My fellow chemists and I appreciate the efforts of this committee on behalf of science and the rewards that research brings.

[The prepared statement of Dr. Isabella Karle follows:]

Testimony of Isabella Karle before the Committee on Science and Technology

U. S. House of Representatives

May 21, 1986

Mr. Chairman and Members of the Committee on Science and Technology: I welcome the opportunity to testify before this Committee with respect to the Government's role in support of scientific research and education. I am honored to have been invited to appear with the American Nobel Laureates for the year of 1985.

My remarks will be general and qualitative and will reflect strong personal impressions from long experience in basic research. Creativity in science, as in other endeavors, is a difficult subject to define or to quantify. Individuals react and operate in various modes. There are, however, some basic requirements that should be fulfilled such as:

1. A good basic education in mathematics and the sciences at all levels of schooling. Exposure of all students to some scientific education is desirable, even necessary, so that the non-scientists can become responsible adults who can respond intelligently to the many issues that arise in our technical society and who can have empathy with the problems facing scientists.

2. An atmosphere of social acceptance and recognition for the scientifically oriented students. The lack of acceptance of the serious students arises in part from too much emphasis in our high schools and colleges on non-academic activities, such as extramural sports.

3. A good environment to stimulate and sustain curiosity about the world around us at all levels of education and in the work place.

4. Reasonable job opportunities and security. Protracted periods of postdoctoral appointments, research associateships and temporary appointments with the resultant disruption of both scientific continuity and of family life have their serious negative effects on morale and productivity.

5. Reasonable and steady funding for research. The nature of research makes it particularly vulnerable to instability. Wide oscillations in funding, and, at worst, interruptions in funding, result in long-term damage such as the dispersal of specialized scientific teams and technical personnel, the delay or abandonment of research programs, and the discouragement of potential students who are highly talented.

Given the above, I would like to discuss two topics in more detail. The first concerns the support of high-risk research which may be defined by no immediate prospect of application or economic returns or even any prospects of solution to the problem. In the spirit of Albert Michelson, the first Nobel Laureate in science from the United States (1907), who performed his first experiments on the velocity of light while an Ensign and an instructor in chemistry and physics at the Naval Academy following his own curiosity, instincts, and motivation, I urge that basic research and exploratory research, that is not particularly focussed on some preconceived goal, receive its share of support.

Our present system of grants has built-in goals and objectives that have the tendency to lead to "safe" research, the kind of research that will satisfy the stated objectives and will insure continued funding. With the constraints imposed by this system, graduate students, postdoctoral researchers and even senior investigators do not really have the freedom to pursue unorthodox and innovative ideas if they do not fall within the stated and approved objectives. Serendipity often plays a

significant role. Scientists may recognize something that may be very important that is not directly related to but stemming from their research. There is the need to divert some of their time and resources to devote to these discoveries or thoughts. As often has been pointed out in the past, "safe" research would have led to a better iron-lung. Innovative research produced the vaccine for poliomyelitis.

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1. "Contemporary Classics in the Life Sciences, Vol. 2, ed. James T. Barnett, ISI Press, Philadelphia (1986).

The second topic that I should like to address is the establishment of a period longer than one year for scientific budgets. The late Philip Handler, Past President of the National Academy of Sciences, was an avid proponent for, at least, a two-year budget period and I should like to re-emphasize the benefits of a longer period for budgets and grants in terms of efficiencies and economies.

1. The time of scientific investigators is extremely valuable to the nation. It should be spent primarily on research (and teaching). At present, principal investigators devote much of their time in the quest for obtaining money to support research. A longer budget or grant period would obviate the frequency of preparation of proposals and/or budgets.

2. The constraint of one-year budget periods in which unexpended funds are lost to the investigator, and, in addition, future funding may be diminished since unexpended funds are viewed as unnecessary funds, make appropriate planning difficult.

Often the acquisition of major equipment is a lengthy process and a one-year period is not sufficient for negotiations, delivery, testing and acceptance. It would also be useful to be able to combine funds from two or more years' allotment for major procurement; an idea of saving for the future advocated by Prof. Modigliani. The needs of a scientific project oscillate. The time of acquisition of equipment or instrumentation is often dictated by the availability of improved models in the relatively near future. An exchange of proposed equipment for a different type of equipment becomes apparent but time constraints of the budget will not allow it. The use of the computer for which charges are made varies depending upon the successes in experimental measurements

in the laboratory. A longer budget period would allow greater flexibility, obviate purchases of inadequate instrumentation that are made to meet budget deadlines, and would result in greater economy in projects where the research results and needs are unpredictable.

My fellow scientists and I appreciate the efforts of this Committee on behalf of science and the rewards to the nation that research brings.

Dr. Isabella Karle, Senior Scientist
Naval Research Laboratory
Washington, D. C.

The CHAIRMAN. Thank you very much.

Just as I predicted at the outset of the meeting, we do have a vote and we will have to take a brief recess while we vote and then we will return and resume with our other distinguished Laureates.

[Recess.]

The CHAIRMAN. If we can resume now and we will begin with Dr. Herbert A. Hauptman, medical science—Medical Foundation of Buffalo in Buffalo, NY.

STATEMENT OF DR. HERBERT A. HAUPTMAN, LAUREATE IN CHEMISTRY, PRESIDENT AND RESEARCH DIRECTOR, MEDICAL FOUNDATION OF BUFFALO, BUFFALO, NY

Dr. HAUPTMAN. Mr. Chairman, members of the committee, carrying out basic scientific research, that is to say, learning as much as possible about the real world, and organizing this knowledge in a meaningful and rational way, is one of the most important activities in which one can engage. Many examples can be cited to justify this claim. Thus, the accidental discovery of x-rays by Rontgen when he observed the darkening of a photographic plate in the vicinity of a stream of electrons made to strike a metal plate had the most important and beneficial consequences for mankind.

Again, the discovery of the CAT scan was the trivial application of a problem in pure mathematics involving the theory of integral transforms and solved in the early part of this century.

Finally, if I may cite my own work, the solution of the phase problem of x-ray crystallography has made possible the determination of some 50,000 molecular structures which constitute the experimental basis of modern structural chemistry.

This work also, among other things, enables the biologist to relate molecular structure with biological activity, permits a deeper understanding of life processes, and makes possible the rational design of drugs in order to treat disease more effectively and with a minimum of adverse side effects.

In all these cases the motivation of the scientists was simply to gather and organize scientific knowledge of the most fundamental kind. His primary interest was not in the applications or the possible long-range consequences of his work which, in any event, could not possibly have been anticipated at the time the work was done.

It is clear from these examples and countless others that basic research in the natural sciences is the essential prerequisite for new technologies and the latter in turn lead to an improvement in the quality of life for everyone.

For this reason, not only is public, that is Federal support of workers engaged in basic scientific research justified, but one can convincingly argue that the failure to supply this support is counterproductive and shortsighted indeed.

At this point I would like to call to your attention two particular disciplines which, because of their central importance and because they have failed, in my opinion, to secure adequate funding in recent years, merit special consideration.

The first of these is mathematics, clearly the most fundamental of the sciences which, because of its abstract nature, exerts a remarkably unifying influence in all areas of science and engineer-

ing. Problems which superficially appear to be of diverse nature often receive identical mathematical formulations so that, for example, the differential equation which describes the motion of a projectile under the influence of gravity is of the same kind as that required to solve an electrical network problem or the simple harmonic oscillator.

Not only are problems in the sciences most accurately and concisely formulated in mathematical terms, but this formulation permits one to apply the powerful solution strategies which the mathematicians have developed over the centuries.

Despite the demonstrated importance and power of the mathematical modes of expression and of thought, support for research in mathematics during recent years has been woefully inadequate, possibly because mathematics appears to be so far removed from everyday life and experience or because even the most intelligent layman often finds it incomprehensible. Probably also the mathematician himself is at least partially responsible because the tendency nowadays toward over-specialization and over-abstraction has caused a breakdown in the channels of communication. Thus, the research mathematician may find that not only does the lay public or physical scientist not understand him but even other mathematicians find his work incomprehensible as well.

The other discipline for which Federal support has flagged in recent years consists of the biomedical sciences. Owing to the ever-increasing cost of conducting research in this area and the ever-increasing cost of the more and more sophisticated equipment needed, the Federal Government has found it difficult, if not impossible, to sustain the momentum of two decades ago when realistic funding levels had been established and were maintained.

Then, too, because of changing priorities, successive administrations have recommended levels of funding which were simply inadequate. For example, the present administration, in common with earlier ones, proposes to eliminate completely the Biomedical Research Support Program of the National Institutes of Health.

This program is used to recruit young faculty, to hold research teams together when funding lapses for a short while, to buy critically needed equipment, and to support pilot projects which, in time, lead to new competing grant applications. In past years the Congress has repeatedly rescued this program from the attempts of successive administrations to scuttle it, but its financial base has been greatly eroded. It should be strengthened, not eliminated, because it performs an essential function.

This committee has shown by past actions that it understands the need for Federal support of basic research in the natural sciences. It has tried to confront the problem of how to distribute support among the various scientific disciplines, when, because of budgetary constraints, the total available support has been severely limited.

I respectfully suggest that the activities of this committee should be focused more on the attempt to secure increased funding for basic research in all the natural sciences by the more intelligent allocation of resources.

Thus, according to published reports, there appear to be many Federal agencies with excessive budgets where appropriate pruning

and more effective management would lead to substantial savings with no loss of efficiency.

I believe that only a small fraction of the savings realized in this way could be used to great advantage to support basic research in the natural sciences.

In summary, then, I would like to see this committee address, as its first priority, the problem of how to secure a larger overall budget for basic scientific research. In deciding how to allocate funds among the different scientific disciplines, I further suggest that the mathematical and biomedical sciences receive special consideration for the reasons already cited.

[The prepared statement of Dr. Hauptman follows:]

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Statement of Dr. Herbert A. Hauptman, 1985 Laureate in chemistry, President and Research Director, Medical Foundation of Buffalo, Buffalo, NY.

Carrying out basic scientific research, that is to say learning as much as possible about the real world, and organizing this knowledge in a meaningful and rational way, is one of the most important activities in which one can engage. Many examples can be cited to justify this claim. Thus the accidental discovery of X-rays by Röntgen when he observed the darkening of a photographic plate in the vicinity of a stream of electrons made to strike a metal plate had the most important and beneficial consequences for mankind. Again the discovery of the CAT scan was the trivial application of a problem in pure mathematics involving the theory of integral transforms and solved in the early part of this century. Finally, if I may cite my own work, the solution of the phase problem of X-ray crystallography has made possible the determination of some 50,000 molecular structures which constitute the experimental basis of modern structural chemistry. This work also, among other things, enables the biologist to relate molecular structure with biological activity, permits a deeper understanding of life processes, and makes possible the rational design of drugs in order to treat disease more effectively and with a minimum of adverse side effects. In all these cases the motivation of the scientist was simply to gather and organize scientific knowledge of the most fundamental kind. His primary interest was not in the applications or the possible

long range consequences of his work which, in any event, could not possibly have been anticipated at the time the work was done. It is clear from these examples and countless others that basic research in the natural sciences is the essential prerequisite for new technologies and the latter in turn lead to an improvement in the quality of life for everyone. For this reason not only is public, that is federal, support of workers engaged in basic scientific research justified, but one can convincingly argue that the failure to supply this support is counterproductive and short sighted indeed.

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and power of the mathematical modes of expression and of thought, support for research in mathematics during recent years has been woefully inadequate, possibly because mathematics appears to be so far removed from everyday life and experience or because even the most intelligent layman often finds it incomprehensible. Probably also the mathematician himself is at least partially responsible because the tendency nowadays toward over specialization and over abstraction has caused a breakdown in the channels of communication. Thus the research mathematician may find that not only does the lay public or physical scientist not understand him but even other mathematicians find his work incomprehensible as well.

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buy critically needed equipment, and to support pilot projects which, in time, lead to new competing grant applications. In past years the Congress has repeatedly rescued this program from the attempts of successive Administrations to scuttle it, but its financial base has been greatly eroded. It should be strengthened, not eliminated, because it performs an essential function.

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The CHAIRMAN. Thank you very much. We will now hear from our final two distinguished Laureates, Dr. Michael Brown, the Department of Molecular Genetics at the University of Texas Science Center, and his collaborator, following him, will be Dr. Joseph Goldstein. But, Dr. Brown, we would be pleased to hear from you at this time.

[Additional information, plus biographical sketchs of Dr. Brown and Dr. Goldstein follow:]

KAROLINSKA INSTITUTET
NOBELFORSAMLINGEN (THE NOBEL ASSEMBLY)
1137N

PRESS RELEASE, OCTOBER 14TH, 1985

The Nobel Assembly at the Karolinska Institute has today decided to award the Nobel Prize in Physiology or Medicine for 1985 jointly to

Michael S. Brown and Joseph L. Goldstein

for their discoveries concerning "The Regulation of Cholesterol Metabolism"

Summary

Michael S. Brown and Joseph L. Goldstein have through their discoveries revolutionized our knowledge about the regulation of cholesterol metabolism and the treatment of diseases caused by abnormally elevated cholesterol levels in the blood. They found that cells on their surfaces have receptors which mediate the uptake of the cholesterol-containing particles called low-density lipoprotein (LDL) that circulate in the blood stream. Brown and Goldstein have discovered that the underlying mechanism to the severe hereditary familial hypercholesterolemia is a complete, or partial, lack of functional LDL-receptors. In normal individuals the uptake of dietary cholesterol inhibits the cells own synthesis of cholesterol. As a consequence the number of LDL-receptors on the cell surface is reduced. This leads to increased levels of cholesterol in the blood which subsequently may accumulate in the wall of arteries causing atherosclerosis and eventually a heart attack or a stroke.

Brown and Goldstein's discoveries have lead to new principles for treatment, and prevention, of atherosclerosis.

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Cholesterol - an important substance

The cholesterol debate during the last decade may have given the public the impression that cholesterol is something you have to avoid to survive. This is, however, neither possible nor desirable: cholesterol is present in all our tissues and is produced in the body. Cholesterol is also vitally important for several of the normal processes in the body.

Cholesterol originates from two main sources - from within through biosynthesis predominantly in the liver, and from without through fat in the food. In the liver as well as in the intestine cholesterol is packeted into particles in such a way that it can be transported in the blood and lymphatic fluid. These particles are called lipoprotein - a combination of fat and proteins. There are different kinds of lipoproteins and they are classified on the basis of their density as determined by ultracentrifugation: Low Density Lipoproteins (LDL), Very Low Density Lipoproteins (VLDL) and High Density Lipoproteins (HDL). The particles transporting cholesterol circulating in the blood are LDL.

LDL, the major cholesterol carrier in the blood, is a spherical particle (Figure 1). Its core consists of some 1,500 cholesteryl esters, each a cholesterol molecule attached by an ester linkage to a long fatty acid chain. The oily core is shielded from the aqueous plasma by a coat composed of unesterified cholesterol, phospholipid and one large protein molecule, apoprotein B. The apoprotein B molecule moors the LDL to specific receptors on the cell surface - the LDL-receptor.

A normal healthy person has approximately 2 g cholesterol per liter plasma. The highest abnormal values, approximately 10 g per liter, are found in persons with a severe disease called familial hypercholesterolemia (FH), which is an inborn error of metabolism.

Cholesterol is found in cell membranes and is converted to hormones and bile acids

Cholesterol has two main functions in the body. It constitutes a structural component in cell membranes, and it is converted to certain steroid hormones and bile salts. More than 90 per cent of the cholesterol in the body is found in cell membranes.

3.

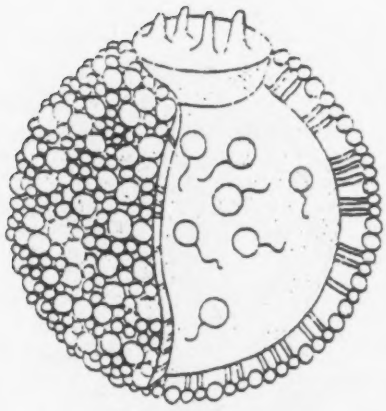

Figure 1. The LDL is a spherical particle with a radius of one millionth millimeter. Most of the cholesterol in the blood stream is found in LDL particles. Its core consists of approximately 1,500 cholesteryl esters, each a cholesterol molecule attached by an ester linkage to a long fatty acid chain. The core is surrounded by a surface coat composed of 800 molecules of phospholipid, 500 molecules of unesterified cholesterol and one large protein molecule, apoprotein B, which moors the LDL to the receptor on the cell surface.

Each cell is surrounded by a membrane, the cell or plasma membrane. Its function is not only to be a protective coat. It also serves as a border control determining which substances are allowed to enter or leave the cell. This function is sometimes facilitated by the presence of specific receptors whereby certain molecules are efficiently trapped and taken up by the cell.

The cells either produce their own cholesterol or take up LDL circulating in the blood stream. The discovery of the LDL-receptor by Brown and Goldstein in 1973 was a milestone in cholesterol research.

Several hormones are produced from cholesterol like estrogen and testosteron, cortison and aldactone. Cholesterol is stored in cells of the adrenals and gonads and can be utilized as soon as there is a requirement for these hormones.

Cholesterol also takes part in the synthesis of vitamin D which prevents development of rickets. Vitamin D is produced in the skin when exposed to the sun's ultraviolet light.

Another vital function of cholesterol is associated with food intake. Cholesterol is converted into bile acids in the liver and is transported via the bile to the upper intestine where the bile salts emulsify the dietary fat making it absorbable. The bile salts then return to the blood stream and are taken up by the liver and again secreted into the upper intestine. This recycling of bile acids normally limits the liver's need for cholesterol.

Excess cholesterol accumulates in the walls of arteries

As stated above cholesterol is of vital importance for the body. Thus, cholesterol deficiency, a rare disease, causes severe damage particularly in the nervous system. However, the most common abnormality in the cholesterol metabolism is of the opposite kind. Excess cholesterol accumulates in the walls of arteries forming bulky plaques that inhibit the blood flow until a clot eventually forms, obstructing the artery and causing a heart attack or stroke.

The accumulation of cholesterol in the arterial walls is a slow process lasting over decades. Among factors contributing and accelerating this process are high blood pressure, a high intake of animal fat in the food, smoking, stress and genetic factors.

Studies on patients with familial hypercholesterolemia (FH) by Michael S. Brown and Joseph L. Goldstein constitute founding stones for our present knowledge concerning the cholesterol metabolism. FH exists in different forms and is inherited as a monogenic dominant trait. Individuals who carry the mutant gene in double dose (homozygotes) are severely affected. Their serum cholesterol levels are five times higher than in healthy persons, and severe atherosclerosis and coronary infarction is seen already in adolescence, or even earlier. Individuals who have inherited only one mutant gene (heterozygotes) develop symptoms later in life - at 35 to 55 years of age. Their cholesterol levels are approximately 2-3 times higher than in normal people.

Patients with FH lack functional LDL-receptors

Brown and Goldstein studied cultured human cells (fibroblasts) from healthy individuals and individuals with FH. Like all animal cells cultured fibroblasts need cholesterol in their cell membranes. Cholesterol - in the form of LDL - was found to be taken up by highly specific

receptor molecules on the cell surface - the LDL-receptor. The revolutionizing discovery was then made that fibroblasts from patients with the most severe form of FH completely lacked functional LDL-receptors. Fibroblasts from patients with the milder form of FH had fewer LDL-receptors than normal - a reduction by half.

Brown and Goldstein also discovered that the synthesis of cholesterol in normal fibroblasts was inhibited when LDL-containing serum was added to the cell culture. Fibroblasts from homozygous patients with FH were not inhibited since they lacked functional LDL-receptors. Consequently their intracellular synthesis could not be influenced.

In later studies Brown and Goldstein showed that LDL which had bound to the receptor was taken up by the cells as a LDL-receptor complex. The receptor is localized on the cell surface in what is called a coated pit. The coated pit invaginates and pinches off to form a coated vesicle (Figure 2). Fusion of several vesicles gives rise to an endosome. The entire process is named receptor-mediated endocytosis. The cholesterol in the LDL particle is released inside the cell. One effect of the uptake of cholesterol is that it inhibits the manufacture of new LDL-receptors on the cell surface. A reduced number of LDL-receptors leads to a diminished LDL uptake. LDL then remains in the blood stream with the risk of accumulation in the arterial walls.

Brown and Goldstein have discovered a new, and unexpected way of regulation of cholesterol metabolism. Normally cells have a high capacity to synthesize their own cholesterol. With a low availability of cholesterol (LDL) in the blood circulation the cells increase the number of LDL-receptors on their surface. The concentration of LDL in the blood is thereby diminished. The more LDL there is in the blood circulation the easier it is for the cells to acquire it. With a high dietary fat intake an excess of LDL circulates in the blood.

<u>The discoveries have resulted in new approaches for the treatment of atherosclerosis</u>

The discovery of the LDL-receptor has broadened our understanding of cholesterol metabolism considerably and explained the mechanism behind familial hypercholesterolemia.

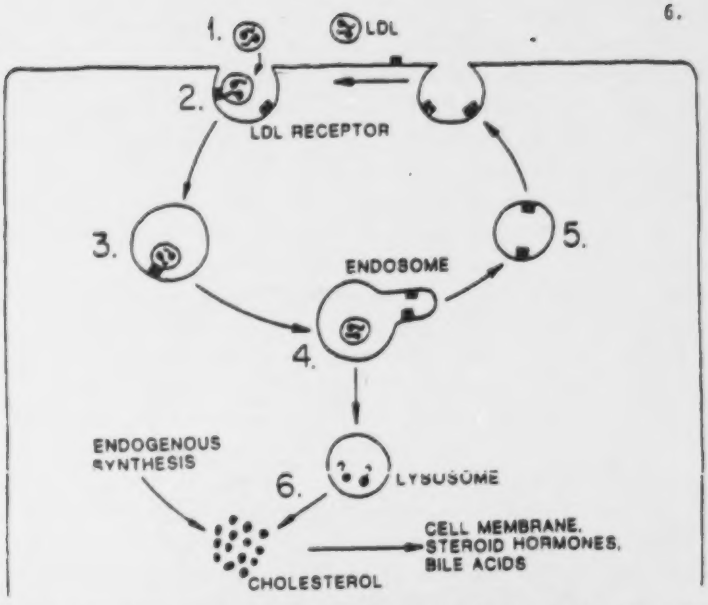

Figure 2. The cells uptake of LDL particles circulating in the blood (1) starts with their mooring to LDL-receptors in coated pits (2) on the cell surface. These pits invaginate and pinch off to form coated vesicles (3). Fusion of vesicles gives rise to an endosome (4) in which the LDL dissociates from the receptor, which is recycled (5) to the surface. The LDL is delivered to a lysosome where the cholesteryl ester is cleaved to yield free cholesterol to be utilized for membrane synthesis or is converted to steroid hormones and bile acids. Cholesterol taken up by the cell inhibits the cell's own cholesterol synthesis.

Brown and Goldstein have used modern molecular biology techniques to show that the LDL-receptor is a glycoprotein located in the cell membrane. Its protein part is constructed by 839 amino acids. Of these 767 are localized on the cell surface, 22 within the membrane and 50 inside the cell in the cytoplasma (Figure 3). The LDL-receptor defect can be one of several different kinds: in some cases the receptor is completely lacking, in others LDL binds poorly, or not at all, to receptor and in still others LDL is bound to the receptor but the LDL-receptor complex is not internalized. Analysis of the LDL-receptor in two patients have shown changes in the intracellularly located protein part of the glycoprotein: in one patient out of the expected number of 50 amino acids only two were present, in another 6 "correct" but 8 "wrong" amino acids were present. The part of the receptor located on the cell surface was unaltered in both patients.

7.

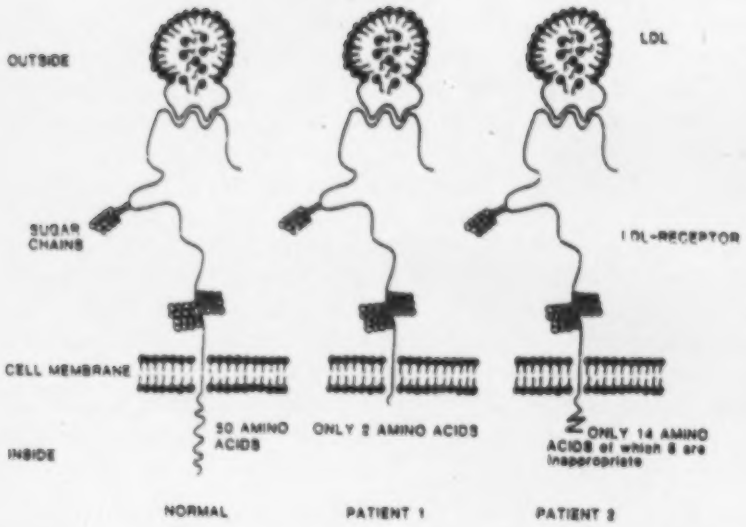

Figure 3. LDL-receptors, one healthy and two abnormal. The part of the receptor localized outside the cell membrane is identical in all three cases. The difference is found in the portion of the receptor inside the cell membrane. The healthy receptor is to the left in the figure. When the LDL via its apoprotein moors to the receptor it is internalized by the normal healthy receptor. The two abnormal receptors are unable to complete the internalization.

The severe form of FH (homozygous) is rare, about one in a million people. The milder form of FH (heterozygous) is much more common, about one in 200-500 people. This means that in a city like Stockholm several thousand inhabitants have the disease with its associated risks of atherosclerosis and heart infarction.

Brown and Goldstein have introduced entirely new principles for treatment of FH based on their discovery of the LDL-receptor. In individuals with the milder heterozygous form of FH the number of LDL-receptors has been increased using drugs - cholestyramine and mevinolin. Such treatment has been found to lower blood cholesterol levels. In the more severe homozygous form of FH, where functional LDL-receptors are missing, medication is no therapeutic alternative. There liver transplantation has been tried. A severely ill 6 year old girl, who already had suffered several heart attacks, was given a new liver and heart simultaneously.

B.

More than six months after the operation her blood cholesterol levels were in the range of 3 g per liter compared to 12 g per liter before the liver transplantation.

The discoveries made by Brown and Goldstein have drastically widened our understanding of the cholesterol metabolism and increased our possibilities to prevent and treat atherosclerosis and heart attacks. But their discoveries have even more far-reaching implications. Coronary infarction is a major cause of death in most industrialized countries. The disease is caused by hereditary and environmental factors, which together cause a reduction of the number of LDL-receptors. This increases the blood levels of LDL and thereby the risk for atherosclerosis. Brown and Goldstein's revolutionary results have widened our horizon and holds promise for future fascinating developments. They speculate themselves about therapy with drugs that increase the number of LDL-receptors simultaneous with a lesser demand for dietary regimens....."it may one day be possible for many people to have their steak and live to enjoy it too".

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KAROLINSKA INSTITUTET
NOBELFÖRSAMLINGEN (THE NOBEL ASSEMBLY)
1133M

October 14th, 1985

NOBEL LAUREATES IN PHYSIOLOGY OR MEDICINE 1985

CURRICULUM VITAE

MICHAEL S. BROWN, born April 13th, 1941 in New York, New York.

Marital Status: Married.

Address: Department of Molecular Genetics, University of Texas Health Science Center at Dallas, 5323 Harry Hines Boulevard, Dallas, Texas 75235, USA

Degrees:

1962	B.A., University of Pennsylvania, Philadelphia
1966	M.D., University of Pennsylvania School of Medicine, Philadelphia

Appointments:

1966-68	Intern and Resident in Medicine, Massachusetts General Hospital, Boston, Massachusetts
1968-70	Clinical Associate, Digestive and Hereditary Disease Branch, National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland
1970-71	Guest Worker, Laboratory of Biochemistry, National Heart Institute, Bethesda, Maryland
1971-74	Assistant Professor of Medicine, University of Texas Southwestern Medical School, Dallas, Texas
1974-76	Associate Professor of Medicine, University of Texas Southwestern Medical School, Dallas, Texas
1976-	Professor of Medicine, University of Texas Southwestern Medical School, Dallas, Texas
1977-	Paul J. Thomas Professor of Genetics and Director of the Center for Genetic Disease, University of Texas Southwestern Medical School, Dallas, Texas

Honorary Degrees:

D.Sc., Rensselaer Polytechnic Institute, 1982
D.Sc., University of Chicago, 1982

Societies and Memberships:

U.S. National Academy of Sciences (elected 1980)
American Academy of Arts and Sciences (elected 1981)
American Society of Biological Chemists
Diplomate, American Board of Internal Medicine
American Society for Clinical Investigation (elected 1974)
Fellow, American College of Physicians
Association of American Physicians (elected 1978)
Phi Beta Kappa
Alpha Omega Alpha

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forts. Brown

Awards:

Proctor and Gamble Scholar, University of Pennsylvania, 1958-62
David L. Drabkin Prize in Biochemistry, University of Pennsylvania, 1962
Fredrick L. Packard Prize in Internal Medicine, University of Pennsylvania, 1966
Established Investigator, American Heart Association, 1974-1977
Heinrich Wieland Prize, for research in lipid metabolism, 1974*
Pfizer Award (formerly Paul-Lewis Award), American Chemical Society, 1976*
Albion O. Bernstein M.D. Award, New York State Medical Society, 1977*
Passano Award, 1978*
Lounsbery Award, U.S. National Academy of Sciences, 1979*
Gairdner Foundation International Award, 1981*
New York Academy of Sciences Award in Biological and Medical Sciences, 1981*
Lita Annenberg Hazen Award, 1982*
V.D. Mattia Award, Roche Institute of Molecular Biology, 1984*
Research Achievement Award, American Heart Association, 1984*
Distinguished Research Award, Association of American Medical Colleges, 1984*
Louisa Gross Horwitz Award, 1984*

Endowed Lectureships:

Harvey Society Lecture, 1977
Carl Moore Lecture, Washington University School of Medicine, St. Louis, MO, 1977
Martin Weiner Memorial Lecture, Brandeis University, 1979
Christian A. Herter Lectures, Johns Hopkins University, Baltimore, MD, 1979
Louis N. Katz Memorial Lecture, Michael Reese Medical Center, 1979
Herman Beerman Lecture, Society of Investigative Dermatology, 1979
Edward F. Bland Lectures, Massachusetts General Hospital, Boston, MA, 1979
Harry Steenbock Lectures, University of Wisconsin at Madison, 1980
Smith, Kline, and French Lectures, University of California, Berkeley, CA, 1981
Duff Memorial Lecture, American Heart Association, 54th Annual Meeting, 1981
Corcoran Memorial Lecture, American Heart Association, 1983
Doisy Lectures, University of Illinois at Urbana-Champaign, 1983

Editorial and Review Boards:

Molecular Cytology Study Section, NIH, 1974-79
Journal of Lipid Research, 1979- present
Journal of Cell Biology, 1981- present
Arteriosclerosis, 1981- present
Board of Scientific Advisors, Jane Coffin Childs Fund, 1980- present

*Co-recipient with Joseph L. Goldstein

JOSEPH L. GOLDSTEIN, born April 18th, 1940 in Sumter, South Carolina, USA

Marital Status: Not married.

Address: Department of Molecular Genetics, University of Texas Health Science Center at Dallas, 5323 Harry Hines Boulevard, Dallas, Texas 75235, USA

Degrees:

1962	B.S., Washington and Lee University, Lexington, VA
1966	M.D., University of Texas Southwestern Medical School, Dallas, Texas

Appointments:

1966-68	Intern and Assistant Resident in Medicine, Massachusetts General Hospital, Boston, Massachusetts
1968-70	Clinical Associate, Laboratory of Biochemical Genetics, National Heart Institute, National Institutes of Health, Bethesda, Maryland
1970-72	Special N.I.H. Fellow, Division of Medical Genetics, Department of Medicine, University of Washington School of Medicine, Seattle, Washington
1972-74	Head, Division of Medical Genetics and Assistant Professor, Department of Internal Medicine, University of Texas Health Science Center at Dallas, Southwestern Medical School, Dallas, Texas
1974-76	Associate Professor of Internal Medicine
1974-	Senior Attending Physician, Parkland Memorial Hospital
1976-	Professor of Internal Medicine
1977-	Professor and Chairman, Department of Molecular Genetics, Paul J. Thomas Professor of Medicine and Genetics, University of Texas Health Science Center at Dallas, Southwestern Medical School
1983-	Non-resident Fellow, The Salk Institute, San Diego, CA

Honorary Degrees:

D.Sc., Rensselaer Polytechnic Institute, 1982
D.Sc., University of Chicago, 1982

Societies and Memberships:

U.S. National Academy of Sciences (elected 1980)
American Academy of Arts and Sciences (elected 1981)
Harvey Society (honorary member 1977)
Association of American Physicians (elected 1978)
American Society for Clinical Investigation (elected 1973)
American College of Physicians (Fellow, elected 1975)
American Federation for Clinical Research
American Society of Human Genetics
American Society of Biological Chemists
American Society for Cell Biology

V.O. Mattia Award, Roche Institute of Molecular Biology, 1984*
Research Achievement Award, American Heart Association, 1984*
Distinguished Research Award, Association of American Medical Colleges, 1984*
Louisa Gross Horwitz Award, 1984*

Endowed Lectureships:

Harvey Society Lecture, 1977
Carl Moore Lecture, Washington University School of Medicine, St. Louis, MO, 1977
George Thorn Lecture, Peter Bent Brigham Hospital, Boston, MA, 1978
Jack Schultz Memorial Lecture, Institute for Cancer Research, Fox Chase, PA, 1978
Christian A. Herter Lectures, Johns Hopkins University, Baltimore, MD, 1979
Edward F. Bland Lectures, Massachusetts General Hospital, Boston, MA, 1979
Mellon Lecture, University of Pittsburgh School of Medicine, 1980
Harry Steenbock Lectures, University of Wisconsin at Madison, 1980
Smith, Kline, and French Lectures, University of California, Berkeley, CA, 1981
Duff Memorial Lecture, American Heart Association, 54th Annual Meeting, 1981
National Institutes of Health Lecture, Bethesda, MD, 1981
Smith, Kline, and French Lectures, Vanderbilt University School of Medicine, Nashville, TN, 1983
Nobel Wiley Jones Memorial Lecture, University of Oregon Health Science Center, Portland, OR, 1983
Corcoran Memorial Lecture, American Heart Association, 1983
Doisy Lectures, University of Illinois at Urbana-Champaign, 1983
Oscar Bodansky Award Lecture, Memorial Sloan-Kettering Cancer Center, New York, NY, 1984

Academic Honors:

Phi Beta Kappa
Alpha Omega Alpha
Summa Cum Laude Graduate and Valedictorian of Washington and Lee University, 1962
USPHS Research Career Development Award, 1972-77
Diplomate, American Board of Internal Medicine, 1972

*Co-recipient with Michael S. Brown

STATEMENTS OF MICHAEL S. BROWN, LAUREATE IN PHYSIOLOGY AND MEDICINE, AND PAUL J. THOMAS PROFESSOR OF GENETICS AND DIRECTOR OF THE CENTER FOR GENETIC DISEASE, DEPARTMENT OF MOLECULAR GENETICS, UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER, DALLAS, TX

Dr. BROWN. Thank you, Mr. Chairman.

I am very honored to have this opportunity to address the committee. And I am also honored to have the opportunity to thank the Congress and the people of the United States for providing the financial support that not only allowed me to receive the training in science that led to our discoveries, but also allowed the universities to exist and for the medical centers to have the facilities to allow this type of research to be conducted.

I would like to urge you not to allow this system, this monumental system, of medical research and education that has been developed in this country over the past 40 years—not to allow that to be dismantled.

Joe Goldstein and I were trained as physicians. We were fully trained and we did internships and residencies in the field of internal medicine, and, indeed, we continued to practice medicine in an academic setting and to teach young students how to become physicians.

But we realized early on in our careers that the really significant advances in medicine could only come from applying the tools of basic science to the clinical problems that we were facing. And so about 15 years ago, when Joe and I came to the University of Texas Health Science Center at Dallas, we began a research program which was focused on the idea of applying basic science tools to the solution of the problem of cholesterol and the way that the reason why some people have high cholesterol levels in their blood and others have low cholesterol levels. And in particular we wanted to know how the genes control the level of cholesterol in blood.

Well, I am not going to summarize the results of those 15 years of investigation because this isn't the proper place. But let me say simply that we were able to determine how the genes control the level of cholesterol and why certain people have an inherited tendency to a high cholesterol level in their blood.

But from the standpoint of this committee, I think the important thing is the way we went about this. Both of us had been trained in basic science as well as internal medicine. We had both spent 2 to 3 years at the National Institutes of Health in Bethesda where we had the opportunity to be exposed to very exceptional fundamental scientists. This juxtaposition of a young, clinically trained physician and a brilliant basic scientist, that combination of individuals has produced the kind of intellectual advance that has led to, not only to our work, but also to all of the major advances in medicine that have taken place over the past 40 years.

You know, medicine has advanced a great deal; 40 years ago, the physician was a spectator in the arena of disease. He could examine his patients. He could watch them closely. He could cheer them on and root for them, but he really couldn't do very much.

Within this scant space of 40 years, that is all changed. Now the physician is no longer a spectator; he is the quarterback of the team. He diagnoses the disease and he designs the perfect offense that is necessary to overcome the problem that he faces.

Those advances, which include a whole variety of new diagnostic tools, a whole variety of new therapeutic drugs, and surgical techniques such as organ transplantation, heart and liver transplantation—all of that has been made possible as a result of fundamental work by basic scientists who lay the foundation for the erection of these large monuments of achievement.

If we don't continue to support the basic science limb of this partnership, if we direct our efforts only at building the superstructures and neglect the strong foundations, the basic science foundations of this effort, then I think the buildings that we erect will have no substance and will be easily destroyed.

So let me say, then, in conclusion, that I would urge this committee that every opportunity that it has to support individuals who are attempting to do basic science, to gather the tools, to gather the knowledge, to uncover the fundamental aspects of biology that will then allow the clinicians, the applied scientists, to use that information for direct practical benefits to mankind.

Thank you.

The CHAIRMAN. Thank you very much.

Dr. Goldstein.

STATEMENT OF DR. JOSEPH L. GOLDSTEIN, LAUREATE IN PHYSIOLOGY AND MEDICINE, AND PROFESSOR AND CHAIRMAN, DEPARTMENT OF MOLECULAR GENETICS, UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER, DALLAS, TX

Dr. GOLDSTEIN. Mr. Chairman, members of the committee:

Thank you for the opportunity to testify before your committee.

Let me begin by just briefly telling you a little bit about the Nobel Prize in physiology and medicine. It was first given in 1901. There have been 85 years of Nobel Prizes in medicine and physiology, and the United States got off to a slow start. The first American-born and American-trained individual to receive a Nobel Prize was Thomas Hunt Morgan in 1933. So the first 33 years—first 32 years—there were no American-born individuals to receive the Nobel Prize. Morgan received the prize for discovering the role that genes played in heredity.

This in a sense was really the beginning of this tradition of genetics in American that has subsequently been honored by many Nobel Prizes.

Well, we have done pretty well since then. In fact, since 1933, we have had 122 laureates. So, all told, from 190—laureates in medicine and physiology—122. Since 1901 to 1985, there have been 122 laureates and 64 actually have come from the United States; 52 percent in the last 85 years have come from the United States. And in the last 20 years—from 1966 to 1985, 67 percent of the laureates in medicine and physiology are American-born and have been trained in the United States.

Well, it turns out that of those individuals who received the Nobel Prize in medicine and physiology, about half are trained as

physicians, M.D.'s, and the other half are trained as Ph.D.'s. And the future of these laureates in medicine and physiology will come from a pool of talented individuals who are currently receiving training grants from our National Institutes of Health and the National Science Foundation.

I would like to concentrate the remainder of my remarks on this idea of training. The single largest agency in the National Institutes of Health that provides training grants is the National Institute of General Medical Sciences. They are responsible for administering two-thirds of all the predoctoral grants—that would be grants to students who are getting an M.D./Ph.D. degree, or grants to individuals who are getting the Ph.D. degree, in areas like genetics, cell biology, molecular biology, or pharmacology.

According to Dr. Charles Miller of the National Institutes of General Medical Scientists, these training grants are facing a real crisis. The funds for the predoctoral training grants and this medical scientist training program that provides money for M.D./Ph.D. trainees has—the funds have been level since 1967, whereas, funds for individual grants—grants given to people like Dr. Brown and me, or Dr. Hauptman, have actually gone up 300 percent over this period of time. So, individual grants to investigators like ourselves has risen, but the funds for grants to trainees has been pretty much level in the last 20 years. And this has really created a big crisis in the sense that now the National Institutes of General Medical Sciences are funding no new programs. And they are having a difficult time actually providing funds to those programs that are currently in existence that are receiving high priorities from the peer review. In fact, there are three very distinguished programs that, according to Dr. Miller, this coming year, will not receive funding, even though they have very high priorities—one at the Rockefeller University in cell biology; two at Columbia University—one in genetics, one in cell biology; one at Cold Spring Harbor and Stonybrook in genetics.

I think that this really is a serious problem, and I would urge your committee to really think very seriously about a redistribution of funds so that these predoctoral training programs can stay in existence, because that's where our major advances in medicine, of the type that Dr. Brown that referred to, will emerge. It is from M.D.'s or Ph.D. trainees who are currently receiving their financial support from institutions like the National Institutes of General Medical Sciences and National Science Foundation.

So in summary, I would like to just again point out that the basis for all medical advances and real true discoveries of the type that will ultimately be acknowledged by a Nobel Prize or that will ultimately improve the health of this country, will emerge from these M.D.'s and Ph.D. trainees who are having a difficult time receiving the proper funding.

Thank you.

The CHAIRMAN. Thank you. Thank you very much, Dr. Goldstein.

On that point, I would like to ask all of you to comment, if you would care to. There has been a good deal of concern expressed about the gradual narrowing of the variety of funding mechanisms that we have used to support scientific research. And the project grant has become kind of the focus of that now. And I guess my

question is: Would the science be served better if we had other mechanisms of support such as sustaining grants, senior investigator grants, block grants, to a group of investigators—maybe across, just of multidisciplinary lines; formerly grants which were used by the Department of Agriculture, primarily, over the years, in addition to just the project grants.

I would be interested—I think all of you have probably been involved in grants, maybe with the exception of Dr. Karle-but I would be interested in your comments about that.

Dr. HAUPTMAN. In that connection, I think one of the things that I would like to see emphasized more—it has already been mentioned here earlier—is to identify, if possible, presumably senior scientists, who have shown by their past performance, that they are about as certain as anyone can be, to perform in the future. I would like to see a real attempt made to identify such people and—and to make long-range grants so that they don't have the problem of coming back. Say, for a 3-year grant, it means that after 2 years only, you have to come back and take all the time and energy that is involved to submit a renewal proposal.

I think one of the things that's been mentioned at NIH is the possibility of a 7-year grant—and I am strongly in favor of that kind of thing. I think identifying individuals and supporting them to a great extent is one thing that I would like to see.

The CHAIRMAN. What about, though, block grants to a group of investigators?

Dr. ISABELLA KARLE. Well——

Dr. HAUPTMAN. Yes, go ahead.

The CHAIRMAN. Dr. Karle?

Dr. ISABELLA KARLE. If I may give some opinions. I think it would be important to have a wide variety of grants. I think that your idea of block grants to a large group of investigators would be very beneficial in many respects. But I think that the small individual grant should also be retained, because there are people who—many scientists—who really work by themselves, or in very small groups. And I think that as far as chemistry is concerned, in the Pimentel Report, if I remember correctly, it was shown that most of the chemistry that has been recognized in this country where there are good results coming forth, is still done in very small groups.

On the other hand, I do agree that there certainly should be block grants to large groups of people who work intimately with each other, even though they may be in different disciplines.

The CHAIRMAN. Dr. Brown?

Dr. BROWN. Yes, I would like to say that I would agree with Dr. Karle that a variety and flexibility is really the key, and that too many constraints on how the money has to be spent really eliminates that flexibility.

I think there are certain cases where groups of investigators should be supported. But I would like to make a special plea for the first research grant of a young investigator who has just finished his training and starting out his career.

In the past, those people, if they had good training and were coming out of good labs, and had a good idea, the study sections at the National Institutes of Health would favor those individuals.

And it would be relatively uncommon for such a person not to be funded.

Now we are in a very desperate situation where the first grant—somebody who spent 6 or 7, or 10 years, training for the moment where he could open his own small laboratory—applies to NIH for a small grant, receives an outstanding priority score, a very strong endorsement by the study section, and then he is not funded.

So, to me, that is a real tragedy. And I think that, of course, we have to support the large laboratories that are very productive and—and have a good record of productivity. But we can't afford to change the system and move the base of funding away from the young investigator with a good idea, because I think those are really the heart—the future of this country.

Dr. HAUPTMAN. Actually, I think NIH does have such a program. The New Investigator Program addresses itself to that very problem. It may not be supported as well as you would like to see it. But at least they have made a beginning there.

The CHAIRMAN. One other question. We have been conducting a science policy task study and looking at science policy for the next 40 years. One of the questions that came before us at one of our last meetings was the problem of honorary authorship in papers. And I am sure as Nobel Laureates you will be invited to participate in that.

Do you see that as a serious problem, or is it a rather isolated problem?

Dr. HAUPTMAN. I am not sure how widespread that problem is. But I am certainly firmly opposed to that idea. I think no one should allow his name to be used as a coauthor unless he himself has made a substantial contribution to the paper in question.

I am not in a position to judge how widespread that practice is. But I certainly know of examples where the—oh, for example, the chairman of a department simply—no paper can be published without his name on it—coming out of that. So I know of examples like that. I don't know how widespread that practice is.

Dr. GOLDSTEIN. I would agree with Dr. Hauptman, that any really good, serious, true scientist will not put his name on a paper that he hasn't been involved in either the actual doing the experiments, or actually the design—the intellectual design—of the experiments.

It is difficult to know how widespread it is. You can't simply count the number of authors on papers in 1986 and compare it to 1976, because medicine and biology is much more complicated and many things do require collaborations today to achieve the goals. But it is a problem, there is no question about it. And I think it is something that your committee should put high on the list of——

The CHAIRMAN. Now, that was one of the suggestions when we were talking, as Dr. Hauptman mentioned, a senior investigator award, that don't be bamboozled by somebody that has a long string of publications that maybe has not participated all of that.

Dr. GOLDSTEIN. But I think a committee—a well constructed committee—would have no difficulty at all in identifying the really outstanding senior investigators that are—should deserve these sort of awards of 7 years.

Dr. HAUPTMAN. I don't know how it is with other people, but I know that I can't possibly be an author or coauthor of, let's say, more than maybe three or four papers in any given year. Now, of course, you find many examples of people who have coauthored maybe dozens of paper in a single year. I think that in itself should raise the red flag to anyone who is studying that.

Dr. JEROME KARLE. I don't really think that it is a widespread problem but I have no sociological study of it.

If I could just take a minute of the committee's time to point out that other cultures, however, do have this problem. I was a witness to a conversation at an international scientific meeting in which some senior investigator was being chided by another gentleman. The senior investigator is from a different country. And he was being chided about the fact that there were some rather freshmen errors in a paper to which he signed his name. And his response, literally, was, I published 80 papers last year. Do you expect me to read all of them? [Laughter.]

This does not happen in this country very often.

The CHAIRMAN. Mr. Boehlert?

Mr. BOEHLERT. At the outset, let me say I think you are sort of preaching to the choir in a way—and you haven't been preaching—but we are on the same wavelength. I haven't heard anything that any of you have said that I would challenge or seriously question. I find myself nodding as you call for a number of things.

The frustration we face is that when we try to go to the floor, for example, with a bill calling—as we did last year— just for a modest increase in funding for the National Science Foundation—had the freeze mentality that said we freeze everything. And we weren't able to get that modest request approved. And this year, again, the President has asked for a modest increase in funding for the National Science Foundation. And this year again it is going to be like pulling teeth.

So, I guess my question is: How do we get their attention? You have got the support you need on this committee, but we need further support on the floor of the House of Representatives. And despite all of our pronouncements on the importance of your work, the support is not going to come over there unless you do a better job—missionary work—across the country. So that individuals are writing to their Representatives urging support for some of the things that you are advocating: Instrumentation, more money for scientific education, and go on and on and on—the list is long.

You are all nodding yes, but let me give you a typical example. I am privileged to represent Cornell. And I will sit in that beautiful oak-paneled dining room at Cornell and see some of the most respected scientists in the country across the table—someone like Ken Wilson, lobbying me. He doesn't have to lobby me. He's got me hook, line, and sinker. But I tell the Cornell people to get their trustees out across the country to write their individual Members of Congress.

Dr. Hauptman.

Dr. HAUPTMAN. In the last analysis, I think—you know, we live in a democracy, and Congress is responsive to the people. And it seems to me that the pressure has to come from the grassroots.

Mr. BOEHLERT. Exactly.

Dr. HAUPTMAN. And in the end, it seems to me that this comes about only by insuring that quality education for everyone is not simply available, but that it actually really takes place. And I think that with an informed electorate, one which has received the education that I think is, not only desirable, but it's really required of broad masses of people in a democracy—democracy such as ours.

I think this is the necessary prerequisite. This is, we have to attack the problem from the ground up. And, I think it's something that's going to take a long time. It is not a problem that's going to be solved overnight. But I think the bottom line is that we need to insure quality education for everyone—really to insure it, not merely to make it available, but to make sure that it takes place.

Mr. BOEHLERT. I agree with you, Doctor. What I am suggesting is that this panel—and I apologize, incidentally, there is as many of us up here as there are, you right down there, and here you are as national resources as Nobel Laureates. But as a matter of fact, we have a little matter on the floor of the House of Representatives called the trade bill. And that has occupied a lot of the time and attention of my colleagues.

I agree with what you are saying, but I would hope in Buffalo, NY, for example, that you are speaking out on this subject——

Dr. HAUPTMAN. We do.

Mr. BOEHLERT [continuing]. Perhaps to editorial board meetings. And all of you, in your respective communities—I think there is a lot of work you have to do to help us help you, if you can follow that through.

Dr. Brown.

Dr. BROWN. One of the problems we have is that scientists are generally not effective spokesmen for their own cause. In fact, there is sort of a negative image within science—if one goes too public in terms of public pronouncements in science, your colleagues tend to worry a little bit about how pure you are.

So there is a built-in negative image. And—a negative incentive not to appeal. Also, there is a danger, because if you appeal on too—too concrete a ground, if you give us this money, we will solve *X* problem in 5 years. Those kinds of things don't work either, because *X* problem might not be solved in 5 years—it might take 10 or 15 years. And then when it is not solved in 5 years, people come back to you and say, how come you haven't solved this problem. And you try to explain, well, we have done a lot of basic research.

The kind of research that I am appealing for is untargeted—you can't identify a problem. You can't say, we will solve that problem 5 years from now. It's very hard. But if you look—for example, let's say that in recent days, an American physician goes over to Moscow to do bone marrow transplants on the Soviet citizens who were affected by radiation. Now, that is a great tribute to American medical science that the Soviets would have an American physician going over there to apply what is the latest state-of-the-art advance in medical scientific technology. Somebody around here ought to take some pride in that in terms of a national achievement. And would just be one very visible thing.

These things can be highlighted and pointed out as practical benefits. But one has to always keep going back and saying, well, how come we can do bone marrow transplantation?

Well, the reason we can do bone marrow transplants is because for the last 20 years people have been learning how bone marrow cells work and how one can understand the biology of the cells. So once you understand that, it becomes possible—the biology of the immune system—it then becomes possible to do the transplants.

Mr. BOEHLERT. Doctor, I guess what I am saying is—and I love that example you have just cited.

Dr. BROWN. Right.

Mr. BOEHLERT. And I would hope that people like you would say to the Dallas newspapers——

Dr. BROWN. Right.

Mr. BOEHLERT [continuing]. I would like an editorial board meeting and I would like to talk to you a little bit about this and what it represents. And so that hopefully in the future when you pick up the editorial, all the Congressmen who happen to live down in the Dallas circulation area will see editorials supporting the very things you are asking us to support—and we do, but we have problems getting our colleagues to support.

You know, we tend to deal with a crisis of yesterday. And we don't, unfortunately, have in Congress too much long-range vision, with the exception, of course, of this committee. [Laughter.]

Dr. HAUPTMAN. I think that a problem that scientists have in that respect is that although we certainly reacted in a favorable way when you ask us, for example to appear here and give our views, I think that we are limited in the pressure that we can apply, because anything that we say sounds self-serving. It seems as if we are saying, yes, we should be supported, and we give reasons for it. But I think everyone says, well, you know, naturally we're asking for support. We would like to get support to do the kind of work that we like to do.

The fact that we like to do it, however, doesn't make it any less important. It can still be worthy of support, but we are not—we can't, I think in the nature of the thing, be our own best spokesmen. The support has to come from people who have no ax to grind, as we do. I think we would all have to admit, we do have an ax to grind, and so we're suspect even though what we say, I believe, objectively, is perfectly valid.

Mr. BOEHLERT. How would you suggest that if Dr. Brown appeared before the editorial board of the Dallas newspapers and seized that opportunity to talk in general terms about——

Dr. HAUPTMAN I agree, I——

Mr. BOEHLERT [continuing] accomplishments. They would be enlightened.

Dr. HAUPTMAN. Yes, I——

Mr. BOEHLERT. One further question and then I'll yield back so we have other colleagues that would like to ask questions.

You know, discussing this trade bill on the floor today—and we are victims—that is, the United States of America—of a trade deficit in the magnitude of $150 billion. Try to enlighten me.

Incidentally, I was a natural for this committee. When I was in high school I got a D in physics, have never taken a scientific or a technical course since then. So when I came to Washington I got assigned to Science and Technology. But I am glad I am here be-

cause it has been part of my education, too, and I am now one of your strongest advocates.

But here is the question I have: Why is it that we are so good, so effective with the basics. We win all the prizes. You are a very distinguished Nobel Laureate, and yet the Japanese are so darned effective in the application. Where are we missing the boat, somehow? Does anybody have any thought on that?

Dr. BROWN. I have thought a lot about the Japanese. [Laughter.]

I have heard the statements of the type that you mention, that somehow the Japanese are skipping the basic research and going right to the application. They are applying the kind—we're making the discoveries; they're applying them, and, therefore, we had better stop making discoveries and apply them.

Mr. BOEHLERT. I am not suggesting that.

Dr. BROWN. But some people say that—some highly placed people in this Government. I think that that is—that the Japanese are starting to get more and more basic. And that at least in the field in which I work, which is the field of genetics, and that involves things like cancer research and things like that, which are genetic problems.

The Japanese are now beginning to publish very, very fundamental articles. True, they started by imitating, by sending students here learning our technology. But now they are doing very fundamental research. So I don't think we can even safely say that we are not threatened at a basic level. We are threatened now at a basic level as well as an application level.

Dr. GOLDSTEIN. There is one thing, though, that may hinder the Japanese. It is that they don't actually have a structure—a training program structured the way we do in the United States. It is difficult for young individuals to obtain training and then become independent. They usually—many of them—have to work for their boss many years, who may put his name on their papers. And so that is one thing that—the chances are the Japanese will imitate our training program. And then when they do that, then we are probably going to be in trouble. Because the real creative ideas will come from young people who are working on things that are not hot at the time——

Mr. BOEHLERT. Excuse me, it is going to become more competitive in the basics.

Dr. GOLDSTEIN. Right.

Mr. BOEHLERT. But we're already in trouble in terms of the application. That's my concern. So you are doing so well—then why don't we follow it through to the logical conclusion? Why do we do everything so great when it comes to the basic and make these great discoveries—and we are so far ahead of the rest of the world, and our scientists get all these awards. And yet the Japanese take the benefit of our research and apply it, and they clobber us in the international marketplace.

Dr. BROWN. Not in medicine. Not in the field that I am in.

Mr. BOEHLERT. I agree.

Dr. BROWN. The Russians didn't call up the Japanese scientists to——

Mr. BOEHLERT. I understand that.

Dr. BROWN [continuing] and do the bone marrow transplants.

Mr. BOEHLERT. And so you are the exception. Let's go a little bit further down the table if we may.

Dr. BROWN. But in the field you were talking about—our expertise is in medicine. That has not happened in medicine.

Dr. HAUPTMAN. I think we shouldn't overlook the possibility that it may be a cultural matter, not only of the Japanese doing this to us. But the Japanese who live in this country—the young Japanese who come and go through the educational system, these are the children who do best nowadays. And I think it may have to do more with culture, then, than anything else.

Dr. JEROME KARLE. I don't really believe that fundamentally the Japanese are any better than we are in anything that we do. I think that what's happening is that we're not doing it. And if one has to ask why aren't we, I certainly don't know all the answers, but I would ask additional questions: What has happened to the work ethic in the United States? Why are industries moving out to other countries and closing down and having U.S. workers sitting on their hands?

These are all aspects of, really, the same question. Why is our educational system on such a low level that we graduate functional illiterates? There has been an obvious deterioration in industrial outlook, in work performance at the workplace, and in the level of education. And I think that whatever it was that had put us in first position—let's say before World War II—in these regards, has somehow deteriorated.

I'm not a sociologist. I don't know all the reasons. But in terms of the fact that we're importing, at an outrageous rate, things that we can perfectly well make ourselves—I have no doubt about that. And there are some outstanding technologies that prevail that are just as complicated as can be. The computer chip development is all ours—it's applied. The airplane business has continued to be first rate. You can find examples of technology that are absolutely first rate and show that we cannot do this.

The fact is that there has been a deterioration of all aspects of, let's say, productivity in our society. And I think that examining the reasons why this has taken place, and also considering what has to be done to motivate people to act differently for industry to come back, for people to really work at the workplace and not do all the things that gave rise to automobiles that didn't function very well in the 1970's and 1980's, and so forth—if we ask those questions, then I think—and can figure out what to do about that, then there is no question in my mind that we are not going to be outdone by anybody.

The CHAIRMAN. Mr. Walgren?

Mr. WALGREN. Thank you, Mr. Chairman.

That is a very interesting exchange. We hope that we can make a contribution to this country doing as well as it possibly can.

The question of funding basic research and the fact that we wish we had more funds to allocate in this area, raises the question of whether or not we should be targeting our funds more. Somebody said that really it is a relatively small number of researchers compared to all that are engaged in the effort—all they are funded—that are really doing the significant work.

Is that your view? Is it—and if that is, does that raise the possibility of our trying to direct funding to a smaller group and not spend funds on some of the scientific efforts that are now being made? Or is it your view that we can't be judgmental about this, that it is the breadth of funding that is most important and that you would not want to see any pullback from the range of funding that's presently being attempted?

Dr. JEROME KARLE. Well, I certainly feel that there should not be any pullback in the range. In fact, I think the range is being too greatly constricted by just the economic forces that are negative at this point.

I also think that it is not possible—that it is a mistake to even try to be too judgmental about how the funds are disbursed, because in its very nature, good creative research is something whose consequences are not easily predicted. And in fact, and our personal lives—I don't know about the doctors, but certainly in the experiences that Dr. Hauptman had, if the research that we did—the support for it—would have been subjected to the judgment of our colleagues in the particular field we worked in, it would never have been carried out.

Mr. WALGREN. Do you believe that we can select areas of scientific endeavor that deserve to be substantially encouraged with funding in areas that are not as potential with progress at any given time?

Dr. JEROME KARLE. Well, I don't know if you were present, sir, when I read my little contribution to——

Mr. WALGREN. No; I was not, I'm sorry.

Dr. JEROME KARLE. I touched on that point. And I pointed out that with all good intentions, questions are often asked with respect to what are the more important activities that are going on. This is a legitimate thing to do. On the other hand, the net consequence of this, as I have observed it over the years, is that what might be emphasized becomes so strongly emphasized that it degrades other important areas of science. And the net consequence is to wipe out activities in fields—and in my own particular field I have seen that happen—the judgments were made. And there are areas in the broad field of crystallography which are simply not being supported now; and professionals were wiped out. There are very few graduate students in this particular area. The degradation has been quite clear.

It is something that has to be done very carefully. There is no question that different emphases are legitimate, but one has to be careful about the way they carry it out.

Mr. WALGREN. Would anyone else like to comment on the idea of narrowing the focus of funding and excluding some of the present recipients of funding?

Dr. GOLDSTEIN. I would like to just elaborate on what Dr. Karle said. For example, I was asked to serve in 1971 when I was a very junior investigator on a committee to plan how one should do research in the broad field of heart disease with the ultimate idea of getting a way to cure atherosclerosis, prevent it, treat it. And in fact, three or four committees meetings were held, big books were written; a lot of money was spent. And basically, today, virtually nothing that people suggested, or the areas of research that we

were working on, because we didn't anticipate that one would have molecular antibodies, gene cloning, all the exciting things one can do.

And so, I think to write a document or to get a committee together to say what areas should be supported and how it should be supported, really is counterproductive. One should really give individual grants, as the members of this panel have suggested, to a large variety of people so they are unrestricted—with the hope that if you give a hundred grants, and one major development occurs from that hundred, then you've accomplished a tremendous thing—one major discovery. Because people will then flock to that area to do research. So scientists will sort of know where the money is once an important discovery has been made.

Mr. WALGREN. Thinking of knowing where the money is, it has been said that many of the real innovative scientists are spending a tremendous amount of their time raising money. And if you have a really bright mind that is the head of a department, it seems a real tragedy to have that person spending perhaps literally 5 of an available 10 hours a day essentially you are writing the same thing over and over and over again trying to find another source to apply for money.

And it is my understanding that the funds are so limited and the interest in applying so broad, that the possibility of succeeding is becoming less and less and less, requiring more and more time to take shots at more and more targets in hopes of hitting just one.

Are we losing a great scientific resource by turning these best of minds into bureaucratic fundraisers?

Dr. JEROME KARLE. Yes, sir. That happened to be another point that I made, and also a point that Mrs. Karle made. An inordinate amount of time is spent on this. And one of the things that I think could be readily done without costing more money or anything of the sort, is to extend the time period over which grants are made, so that this is not quite such a recurrent phenomenon on the time scale. But that's of course, only one aspect of it.

Mr. WALGREN. But that would say that the individual project grant probably is what is taking up a lot of time and applications when you want to get more of your money into other forums than that.

Dr. HAUPTMAN. No, I don't agree with that. I think the individual project grant is a most important one to maintain. I think it's the individual research or the outstanding individual researcher who has to be identified as soon as possible, and he is the one who should receive major support without requiring him to come back every 2 or 3 years and rework in order to renew whatever he has to have.

Mr. WALGREN. So you would just suggest lengthening the——

Dr. HAUPTMAN. I would strongly——

Mr. WALGREN [continuing] definition of the project so the funding flows to an individual researcher——

Dr. HAUPTMAN. The individual, I think——

Mr. WALGREN [continuing] is recognized up to a certain point.

Dr. HAUPTMAN [continuing]. Is the most important—is the key here, that it is the individual—the really outstanding individual who has to be identified and who must then be essentially free to

go on his way without requiring all these renewal applications every 2 or 3 years, without requiring all these progress reports. I mean, all these things, for him, are just a waste of time.

And I also want to endorse what Joe Goldstein just said a few minutes ago. I think if any one thing has come out of this hearing today, it is the essential characteristic of basic research that you just don't know what the ultimate fruits will be.

I think a perfect example of that is the discovery of x rays. If Rontgen had been asked some hundred years or so ago to devise a scheme, let's say, for looking inside the human body, he would never, never have come up with the discovery of x rays. His discovery of the x rays was purely a result of scientific curiosity, and it turned out to be one of the most beneficial things that ever happened to humankind. And I think it's no accident.

This is the character of basic research. And it is the outstanding basic researcher who should be supported just to gather knowledge, just to collect fundamental knowledge, and others will find ways to use that, to transform that into useful—useful technologies.

Mr. WALGREN [presiding]. The gentleman from Pennsylvania, Mr. Walker.

Mr. WALKER. I thank the other gentleman from Pennsylvania. We have turned it into kind of a Pennsylvania hearing at the moment here, but I thank you.

I think this has been very interesting. I am sorry I wasn't here for some of the beginning.

But let me start off with a question by asking, How much money do you think the Government would have to come up with to fund all the research that ought to be done right now by all the scientists ?

Dr. HAUPTMAN. Dr. Eric Block, the Director of NSF, has come up with a number. I think he's recommended an increase of 50 percent, Federal support, for basic scientific research.

Mr. WALKER. That would get us to a—somewhere in the range of $2 billion, is that—is that right?

Dr. HAUPTMAN. I believe this is what Dr. Block was talking about, yes.

Mr. WALKER. So we would be talking, as a nation, probably somewhere in the vicinity of $5 billion, then; is that right?

Mr. WALGREN. Basic research is suggested at about $12 billion.

Mr. WALKER. $12 billion?

Mr. WALGREN. And so if we were to double it, you would be——

Mr. WALKER. $24 billion.

Mr. WALGREN. Adding another $12 billion.

Mr. WALKER. OK. Well, the only reason why I asked the question is, that my guess is that even if we came up with that kind of money, that you would still have, then, a selectivity process that would have to—it would have to come in. I mean, even if we did everything we are going to do, you have a certain amount of selectivity that would have to go into it.

The problem is, if you get to all of the money that could possibly be spent, you would probably be then outside the realm of peer review, because everybody would be getting all the money that they ever wanted for their projects. I mean, that's essentially the question.

And so, what you would get then is a political review process. And I guess what I'd like—I would like to have you comment on is, you know, what—how do we manage the system? As long as you have scarce resources, my guess is that you are going to have to have some sort of peer review process.

I heard Dr. Karle say here a minute ago that even peer review might have some problems with it, I gather, because he was saying that your research probably would not have been endorsed by peers if that was the only method of selection.

Dr. HAUPTMAN. To put it mildly, that is true.

Dr. JEROME KARLE. It wasn't—it wasn't the——

Mr. WALKER. It was not?

Dr. JEROME KARLE [continuing]. Even though nobody—that it didn't intrude on their funding.

Mr. WALKER. And yet, I would assume that you would also disagree with the process that has sometimes happened—thank goodness, irregularly around here, but it nevertheless has happened where Congress has totally gone outside the peer review process and just decided that there is some university research project that happens to be in a district where somebody has some political clout, and so, therefore, we are going to put the money in there regardless of what the peer review process is.

I assume that most of you would have some reservations about that kind of process.

Dr. HAUPTMAN. That is surely a big mistake.

Dr. JEROME KARLE. Yes.

Dr. HAUPTMAN. I don't think anyone here would disagree with that.

Dr. BROWN. Let me just speak up in favor of peer review. I think that it is like democracy—it's not the perfect system, but nobody's devised anything that's any—can compare it—with it at all. So, if granted that you might not have been funded by your peers, but it would—might have been very hard to find somebody who would have funded it, period.

So, I mean the fact is that obviously there are always going to be people with brilliant ideas who are not funded. That there is no way that anyone can even imagine of changing that, short of having infinite amount of money. You are right, there have to be limits.

The argument that we are making now is that the limits are much too tight. There are very, very good scientists who would be accepted not only by peers, but by every other objective criterion, and who are begging for funding right now. It is—the pinch is beginning to be felt in a very strong way.

Mr. WALKER. I guess I agree with that. But my concern is that—and I just thought I would raise the questions with a distinguished panel such as yourself—is that any time we set up these mechanisms for attempting to be selective, and particularly when we are being selective in areas such as basic research, the processes themselves tend to take on a life of their own; that we tend to appoint to peer review panels people who have distinguished themselves in certain fields. And so, therefore, in their selective process, they tend to approve money for things that they are knowledgeable about, and that is understandable.

And yet if you move outside that, and you move over and allow the bureaucrats to do it, the bureaucrats will do it based upon some kind of a criteria that they artificially establish.

If you let the politicians do it, anything that's hot at the moment—the headline at that moment—will be where we will direct the money.

And, Dr. Karle, I think the point you were making here a few minutes ago is a very good one, that kind of stuck in my mind, is we will abandon virtually all kinds of research in order to put all the money—take all the money and put it toward something that happens to be capturing the headlines at any particular moment. I mean, that is essentially political decisionmaking.

Is there some better system? Is there some way of assuring that when you have scarce resources that we do an adequate job of selecting what is best—not necessarily what is best in an applied sense, but what is likely to move us the furthest in terms of basic research? Dr. Goldstein?

Dr. GOLDSTEIN. OK, let's assume you do have a limited number of resources, and you do have to apply selectivity, which I agree—if you don't apply selectivity, no matter how much money you have, you will get mediocrity. There is no question about that.

So I think that one has to make a first priority these individual research grants to the individual, not to groups, but to an individual, in sort of an unstructured way—a very broad net is cast. And then one has to have training grants. OK, there is no question about that, because the future researchers who will apply for the research grants are going to be the trainees.

And the area that one has to look carefully at are these large program projects, these programmatic areas that are sort of given—between the bureaucrats and peer review, a lot of the programs—programmatic grants, the huge grants, given by the NIH, are—even though there is a peer review, there's also a bureaucratic element, too.

Those are the ones that need to have close scrutiny. Some of those are really outstanding, some are mediocre, and some are poor. And that is the area that I would——

Mr. WALKER. How do we as politicians decide between those three? I mean, I think you are right.

Dr. GOLDSTEIN. I think you have to have good peer review committees that advise you.

Mr. WALKER. You heard from my colleague from New York who said he got lousy grades in science; so did I. I am here making the policy decisions, but, you know, one reason why we do that is because we bring to it a kind of different mentality about it. I think that is a plus, when all is said and done. But it still is a question of how do we decide in some of those big programs that some of them are lousy, some of them are very good, and some are——

Dr. GOLDSTEIN. I think you have to go to the Director of the NIH, Dr. Weingarten, and say, we have to examine these areas, and ask him to come up with a blue ribbon committee to look into this. That is one way of doing it.

But that would be the area—that is assuming, you know, tight resources. I think all of us would agree that we have to have training grants, and we have to have individual grants. So one is left

with the one area that is fuzzy, and these are these programmatic areas that are large. Some of them are given to five or six individuals, others go to hundreds of individuals.

Mr. WALGREN. I was going to wonder, would the gentleman yield, whether we know off the top of our heads the balance between the individual grants and the training grants on the one side, and what might be categorized institutional research funded on the other. Is it 50–50 at this point? Perhaps what's bringing the problem is that as you want more individuals as the stress becomes greater there, we envy the other direction of money more. I question what the balance is there.

Mr. WALKER. My guess is that the bigger the program, the more likely it is to keep its funding simply because the large nature of it makes it something that keeps moving along, whereas, the individual is out fighting for himself in many of these instances. And we find it easier to deal with cutting individual grants, or just stopping individual grants than we do stopping major programs that are ongoing.

Just one other thing. I would just be interested in your comments on the whole thing that was raised at a U.S. News and World Report article here of a week or so ago of emerging in our society of hi-tech anxiety. The whole point, that some of the things that are happening in science today are really giving people a sense of anxiety about the future, that we don't know how to manage all of the things we are creating in science.

I would just appreciate a comment from some of you, because I think for those of us who are concerned about future development, we also have to bring a public along that sometimes is concerned about some of the very things we are creating. Some of you who are working in genetics, I think, would probably be particularly sensitive to that at the present time.

Dr. BROWN. I think my own view is that technology and understanding—fundamental understanding—is our strongest security blanket. If we understand something, we can feel secure about it. It is only the lack of knowledge that gives us a misunderstanding.

I can just point to one example—that is the AID's virus. If we didn't have the capacity to understand that AID's is caused by a virus with a certain gene and within a very short time, that virus has been isolated, the gene has been isolated. And as scientists, we feel comfortable that we know what we are dealing with. Imagine if we didn't have that technology and suddenly along comes this plague—all of the fears would be infinitely greater than they are now.

So by applying science, we are actually reassuring people, at least, about some of the biology of the AID's virus. We know what we are dealing with. I feel much more secure.

When Legionnaire's disease developed in Pennsylvania—I might add——

Mr. WALKER. We remember it well.

Dr. BROWN. I just spoke at the commencement of the University of Pennsylvania yesterday—Monday.

But anyway, when Legionnaire's disease developed, there was a sense of panic, initially, because it didn't seem to be fitting the model of any known bacterial or viral disease. People seemed to be

coming down with it in a very fuzzy way, there wasn't any consistent pattern. For a while, there was a kind of insecurity.

But the minute it could be discovered to be a bacterium, and a slightly more unusual one, but a bacterium, nevertheless, and it would respond to certain antibiotics, then all of the anxiety disappeared.

So my view is that technology and knowledge is the safest thing we have to prevent anxiety.

Mr. WALKER. I think that is a good answer, I appreciate it.

Dr. Karle.

Dr. ISABELLA KARLE. If we do not develop this knowledge in our country, it will be developed elsewhere. So, we in our country, would be ignorant of such knowledge and then there would be real anxiety if some of the less attractive results from science would start being applied elsewhere. So there is no way out—we have to study these things. We have to at least try to be first, if we can.

Mr. WALKER. My understanding—and we do have a vote here—but my understanding of the situation in dealing with most people—I live next door to Three Mile Island. There was hi-tech anxiety, also, for many people. It is not so much that people, I don't believe, are saying that we should not be on the leading edge in creating these things.

The question that people have is, having created it, do we know how to manage it. Do we have a capability of managing all the things that we are creating scientifically. That really is, to some extent, outside your fields—you are in the process of creating. Somebody else has to figure out how to manage.

But the point is, can you, as scientists, give some confidence to people that in fact the management is something which is possible along the line? I think managing disease and so on is certainly one answer to that.

Dr. Karle.

Dr. JEROME KARLE. I get the impression from most of these dramatic accidents that occur, that we read about, that upset people so much, that they occur, not because of potential incompetence in dealing with the problems, as much as it is irresponsibility—that there are simple things could have been done; any number of situations in which there were bad accidents, but they simply weren't done.

That is a cultural and sociological problem. In some respects we have to make more responsible and more careful people in our society. This is education, this is bringing people up properly.

Mr. WALKER. It goes back to your work ethic and productivity point to a large extent.

Dr. JEROME KARLE. Exactly.

Mr. WALKER. Thank you, Mr. Chairman.

Mr. WALGREN. And, I am sure, leads us to emphasize the importance of research in the social sciences as well, which is an area that has been generally turned away from by our Government funding system, and yet, holds a key to such a broad area of improvement.

Unless there is a rebuttal to that, we want to thank you very much for your contribution to this discussion. We appreciate your being a resource, not only to the society, but to us as well. I want

to express our appreciation for your coming today. Thank you very much.

Dr. BROWN. Thank you.

Dr. HAUPTMAN. Thank you very much.

Dr. GOLDSTEIN. Thank you.

Dr. JEROME KARLE. Thank you.

Dr. ISABELLA KARLE. Thank you.

Mr. WALGREN. The committee is adjourned.

[Whereupon, at 4:05 p.m., the committee adjourned, to reconvene subject to the call of the Chair.]

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